
بسم الله الرحمن الرحیم

Multiple sclerosis & Molecular Therapy

Qazvin University of Medical Sciences

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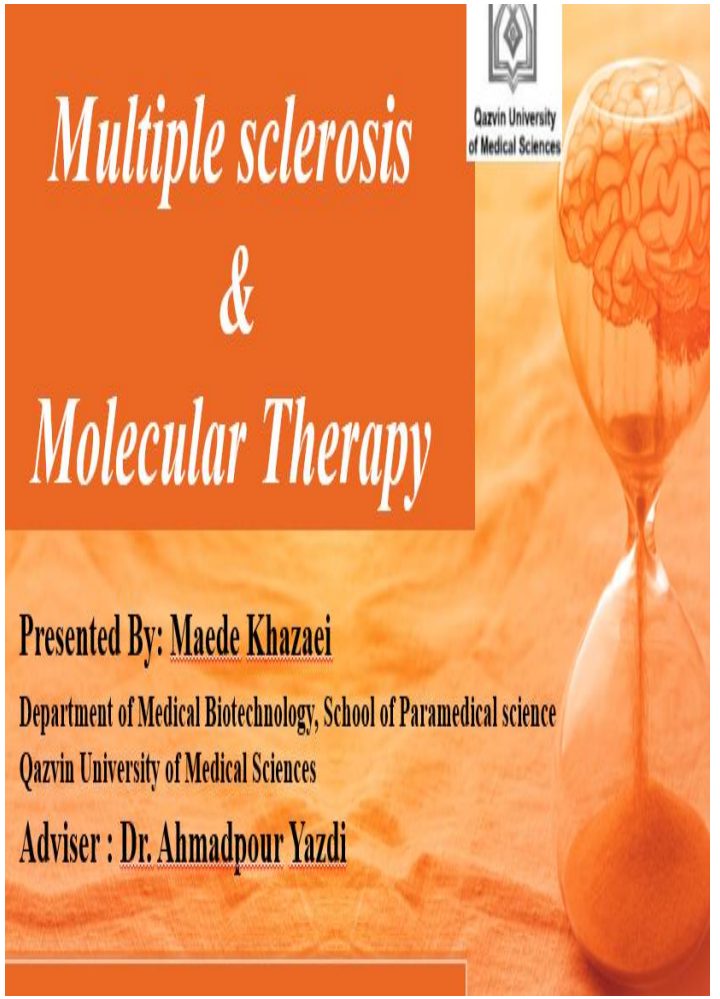
Advisor : Dr. Ahmadpour Yazdi

Content:

- History & review on M.S
- Molecular Mechanism
- Etiology → Genetics
  Environment element
- Diagnosis

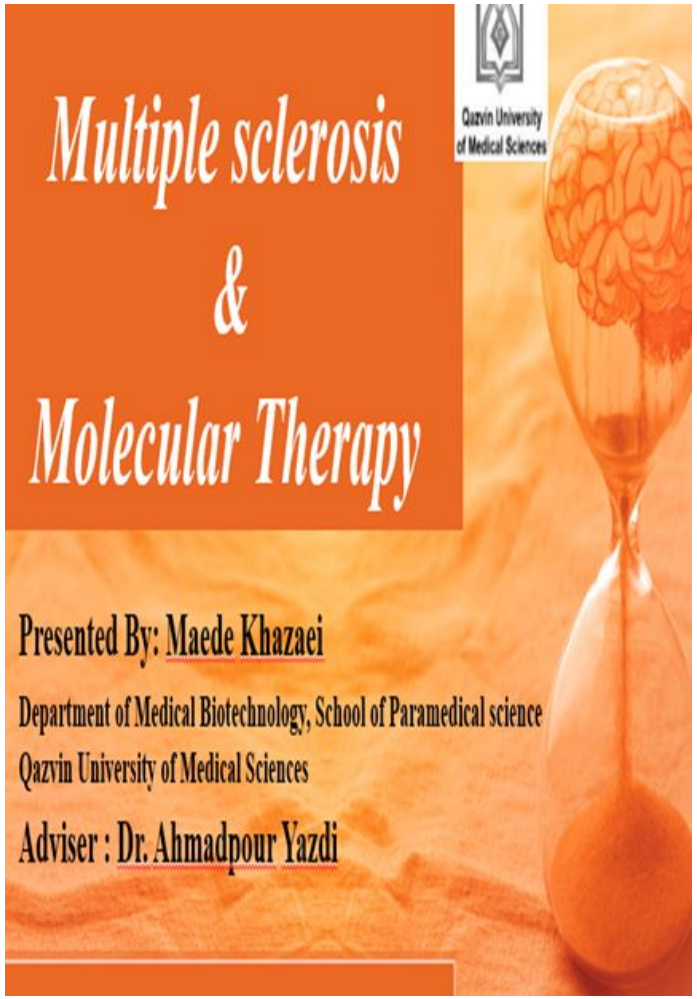


Content:

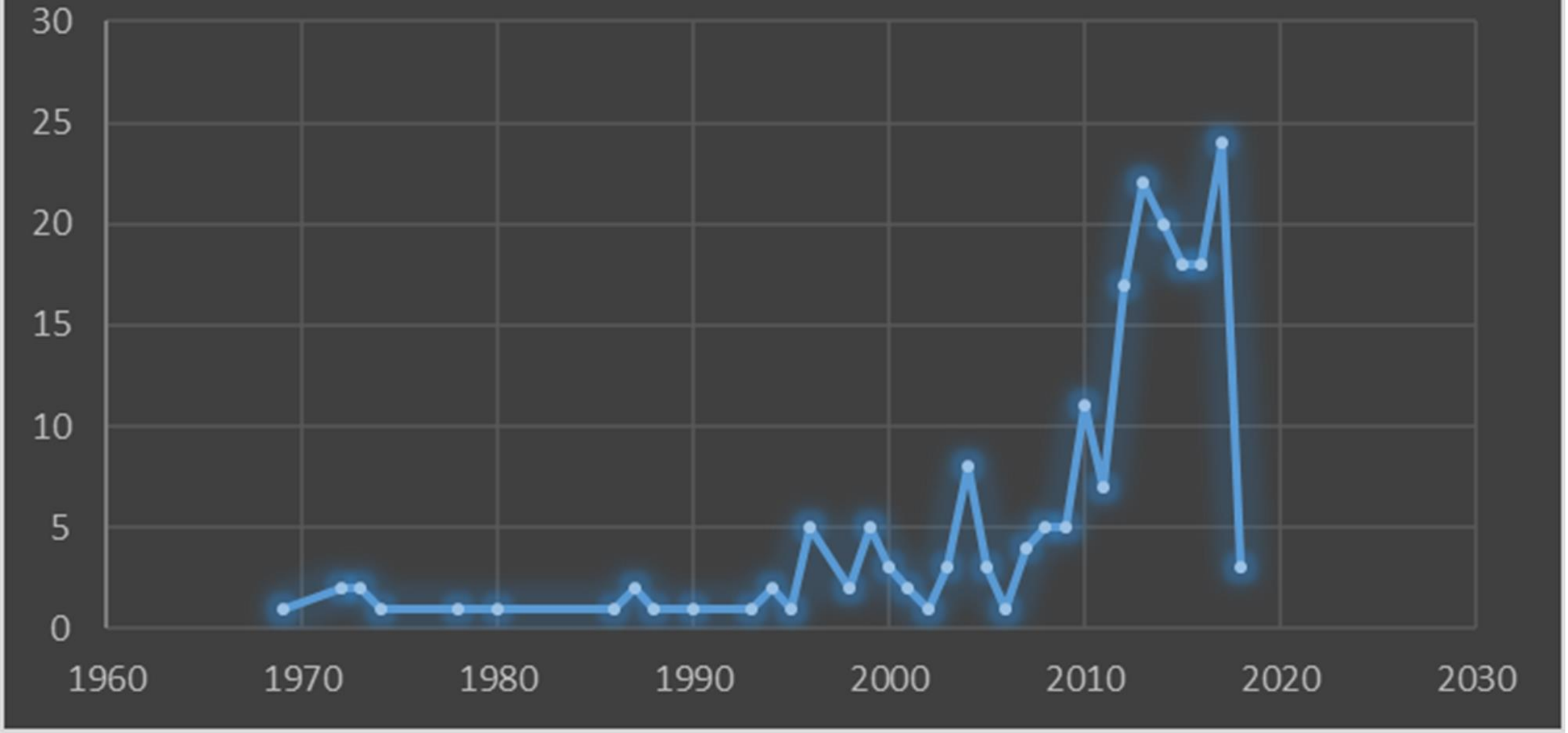
- Therapy → **Molecular**

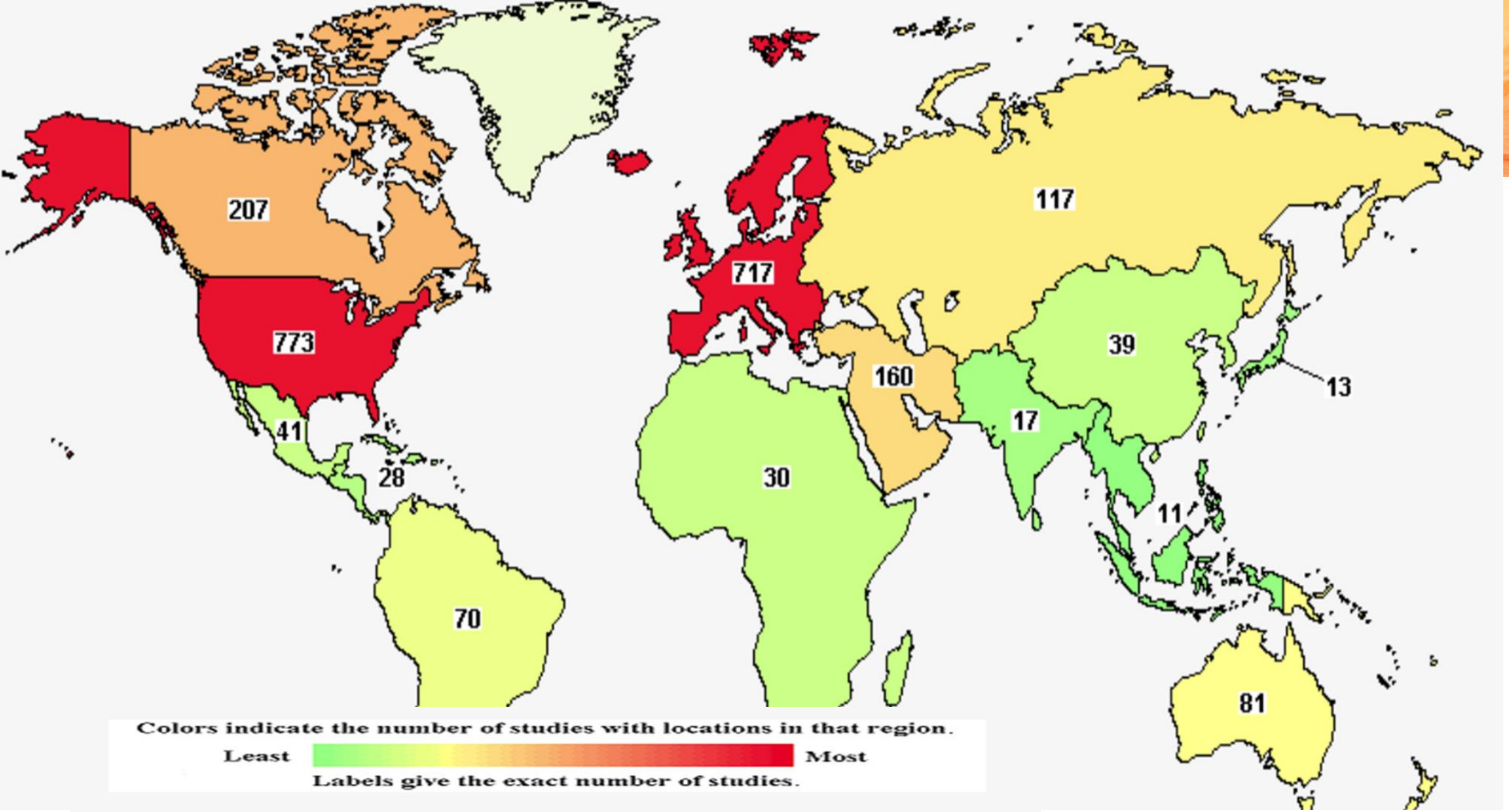
  Non Molecular

- Conclusion
- References



pubmed - (("Multiple Sclerosis"[Mesh]) count

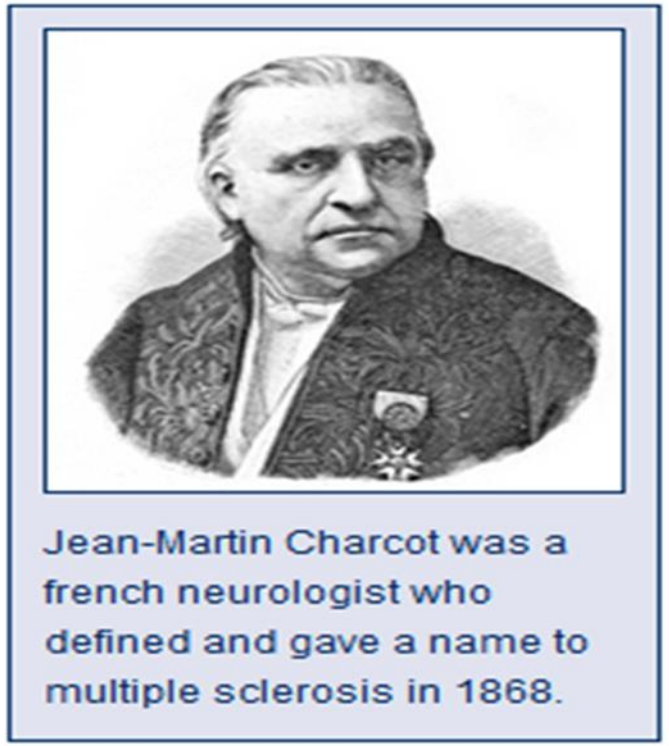




clinicaltrials.gov/ct2/results/map?cond=Multiple+Sclerosis&map, dated Nov.22.2018

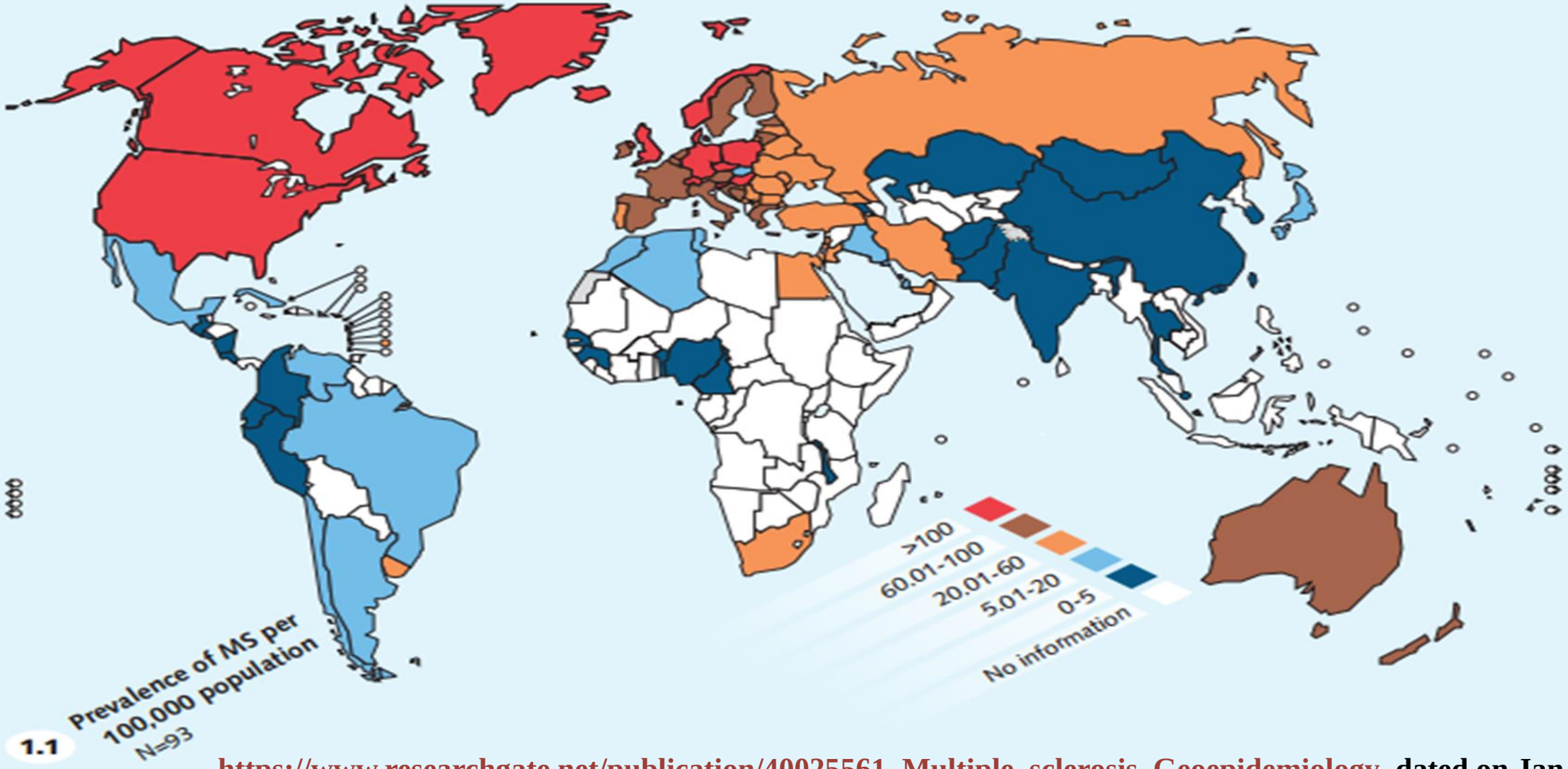
History & Review on M.S

- The first one on 1940s.
- Jean-Martin Charcot
- The first drug was used: Cortisol
- disease-modifying therapies (DMTs)
- Affects young to middle- aged adults
- Women affected more than men



https://fa.wikipedia.org/wiki
dated on Dec.5.2018

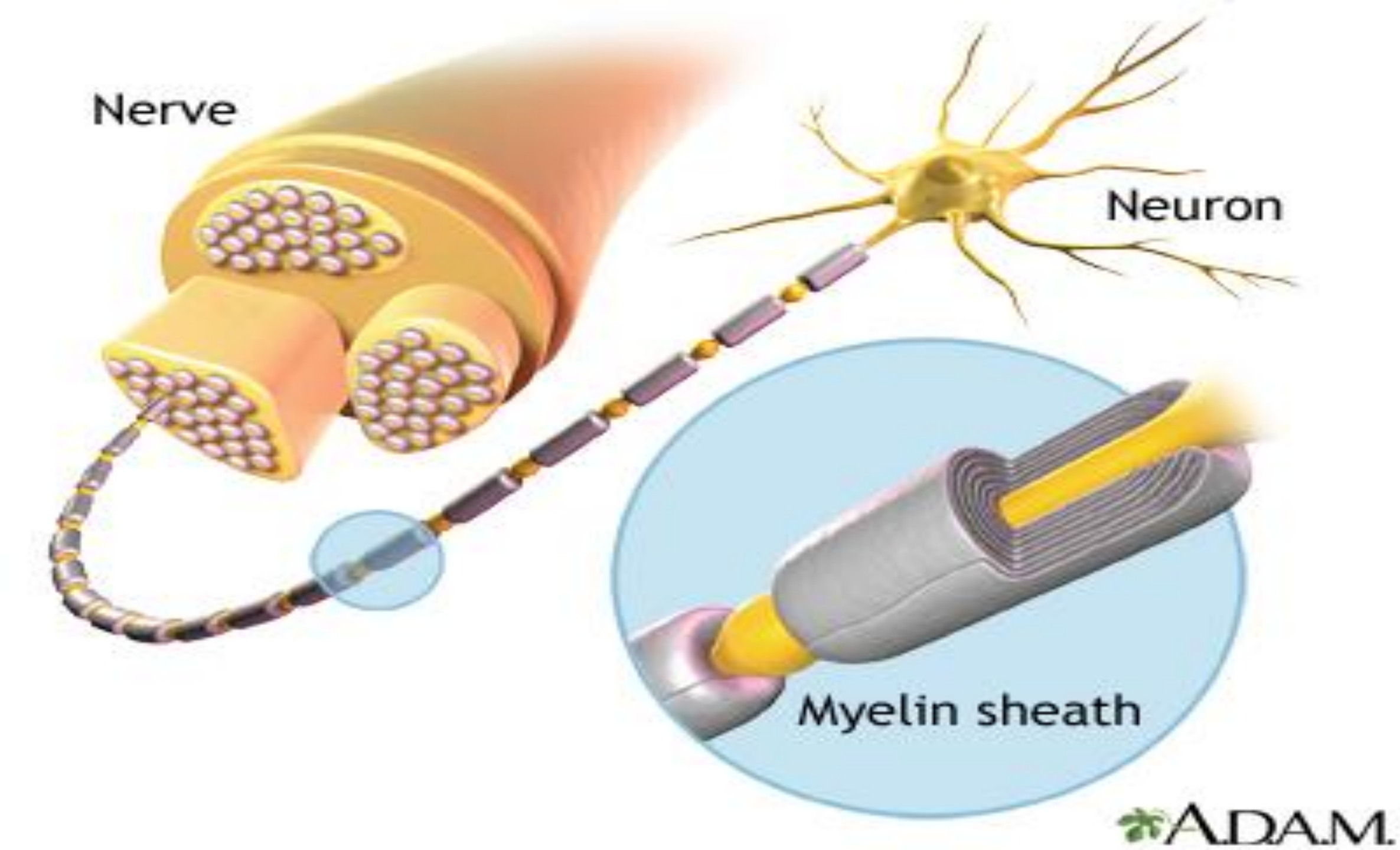
Prevalence :



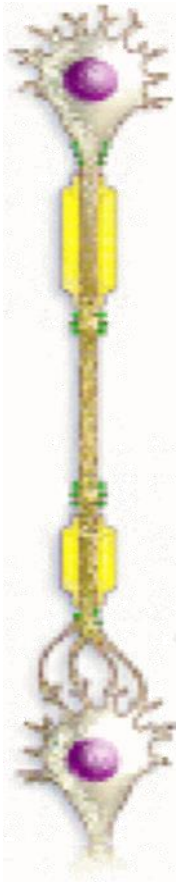
https://www.researchgate.net/publication/40025561_Multiple_sclerosis_Geoepidemiology, dated on Jan.1.2019

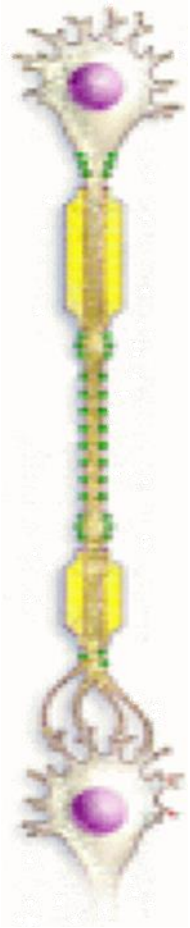
Pathogenesis of MS

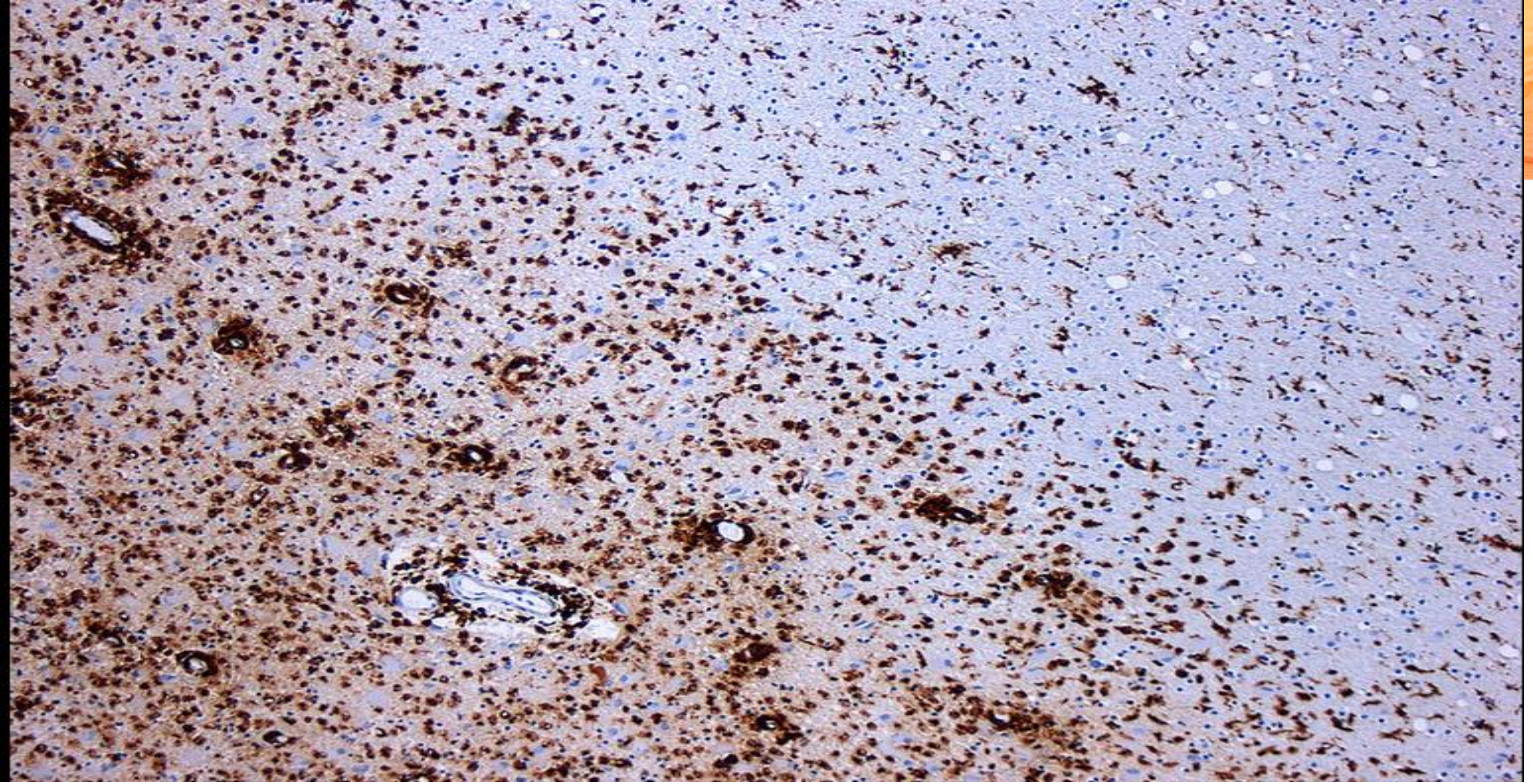
- Myelin sheath
- Segmented **lamination** that **wraps axons** of many nerve cells
- **Increases** velocity of **nerve impulse conduction** in the axons
- Composed of **myelin**, a substance with **high lipid content**
- Characterized by chronic **inflammation**, **demyelination**, and **gliosis** (scarring) in the CNS
- **Subsequent antigen-antibody** reaction leads to demyelination of axons


Nerve
Neuron
Myelin sheath
A.D.A.M.

What happens to the myelin and nerve fibers?



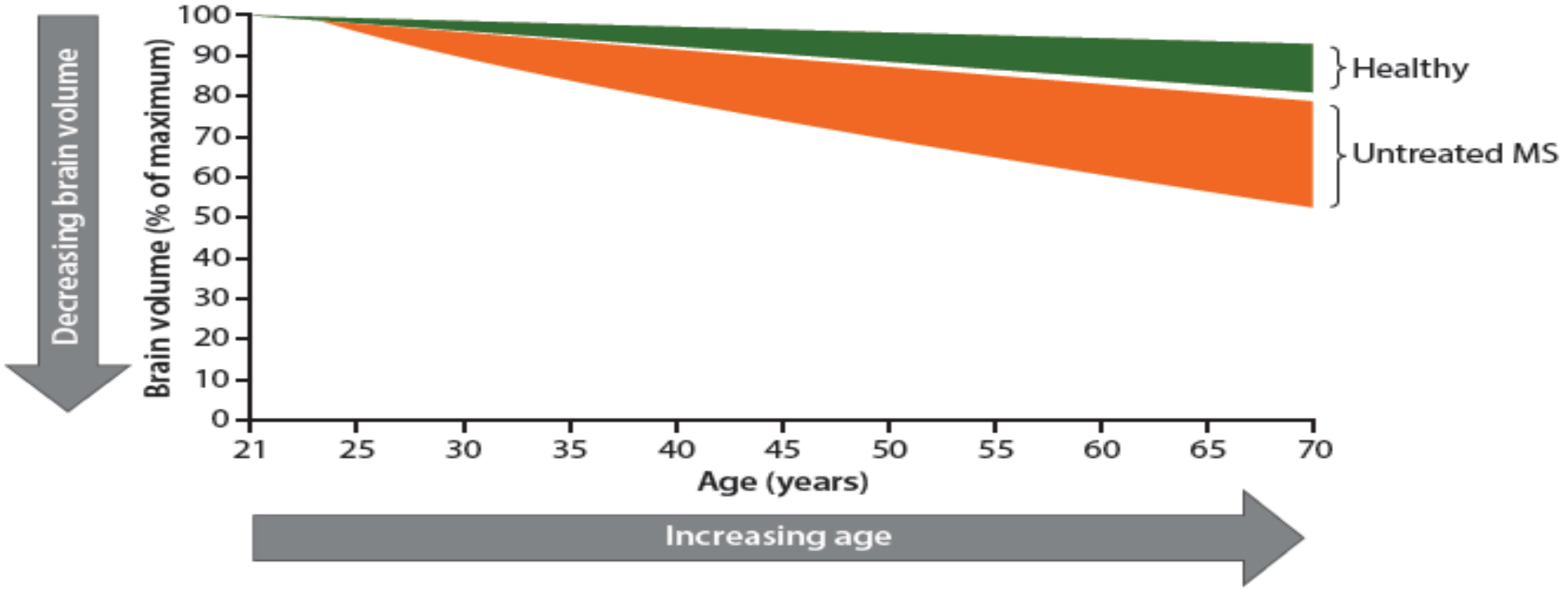




plaques scattered throughout the CNS

https://fa.wikipedia.org/wiki, dated on Dec. 5. 2018

Disease activity persists: brain atrophy is accelerated



This example illustrates how brain atrophy may be accelerated in a person with untreated MS, with disease onset at 25 years of age, compared with a healthy individual

Figure reproduced with permission from Oxford PharmaGenesis from Giovannoni G *et al.* Brain health: time matters in multiple sclerosis.

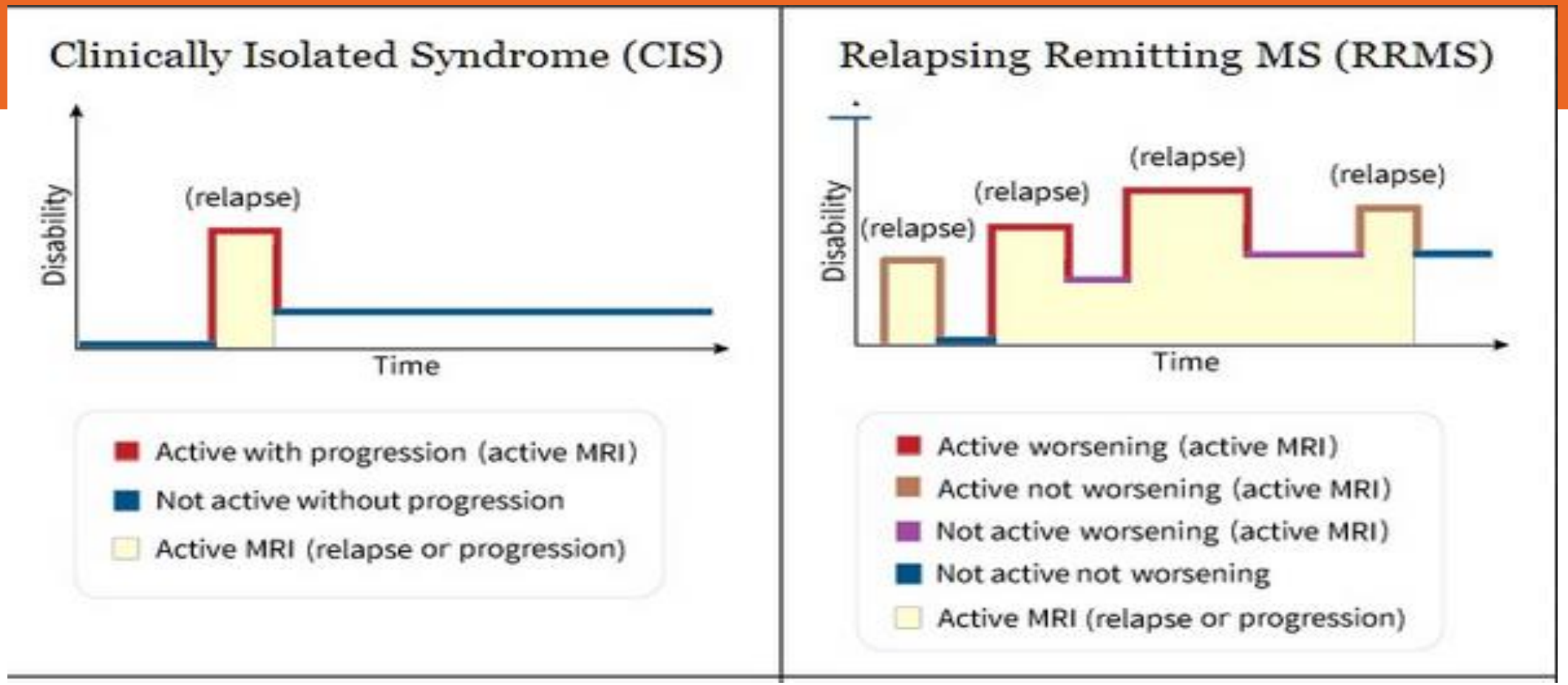
Four Major Varieties of MS

- Clinically Isolated Syndrome (**CIS**)

1. shows characteristics of inflammatory demyelination

- Relapsing-Remitting Multiple Sclerosis (**RRMS**)

1. with progressive worsening of nerve functions with each attack
2. Accounts for 85% of MS patients



https://my-ms.org/ms_types.htm/**dated on Dec. 5.2018**

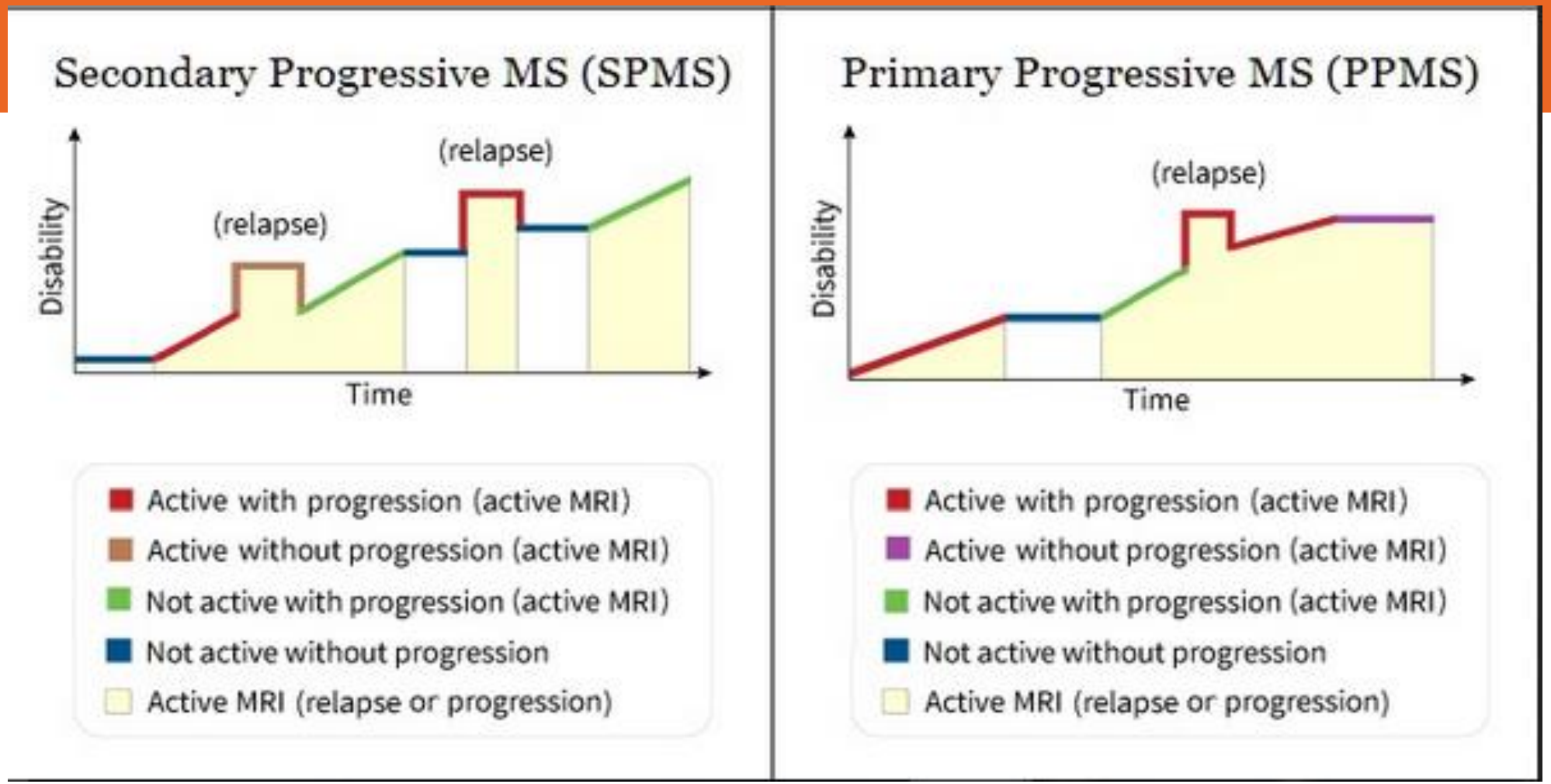
Four Major Varieties of MS

- Secondary Progressive Multiple Sclerosis (**SPMS**)

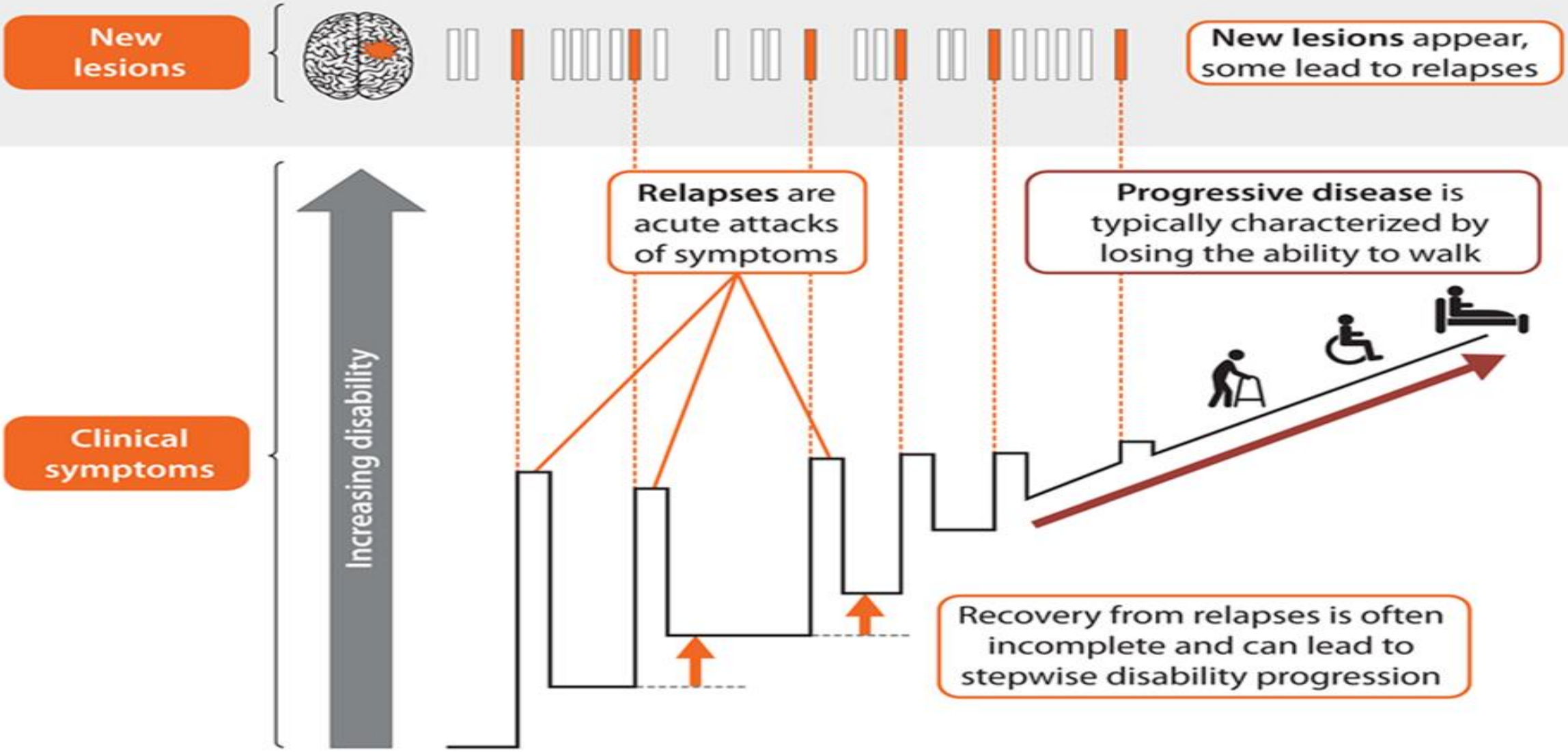
1. Initial period of relapsing-remitting, then steady worsening of disease
2. 50% of patients diagnosed with RRMS develop into this variety within 10 yrs without drug treatment

- Primary-Progressive Multiple Sclerosis (**PPMS**)

1. characterized by worsening neurologic function
2. Slow continuous worsening of disease from onset
3. Only about 10%



https://my-ms.org/ms_types.htm/ dated on De. 5.2018



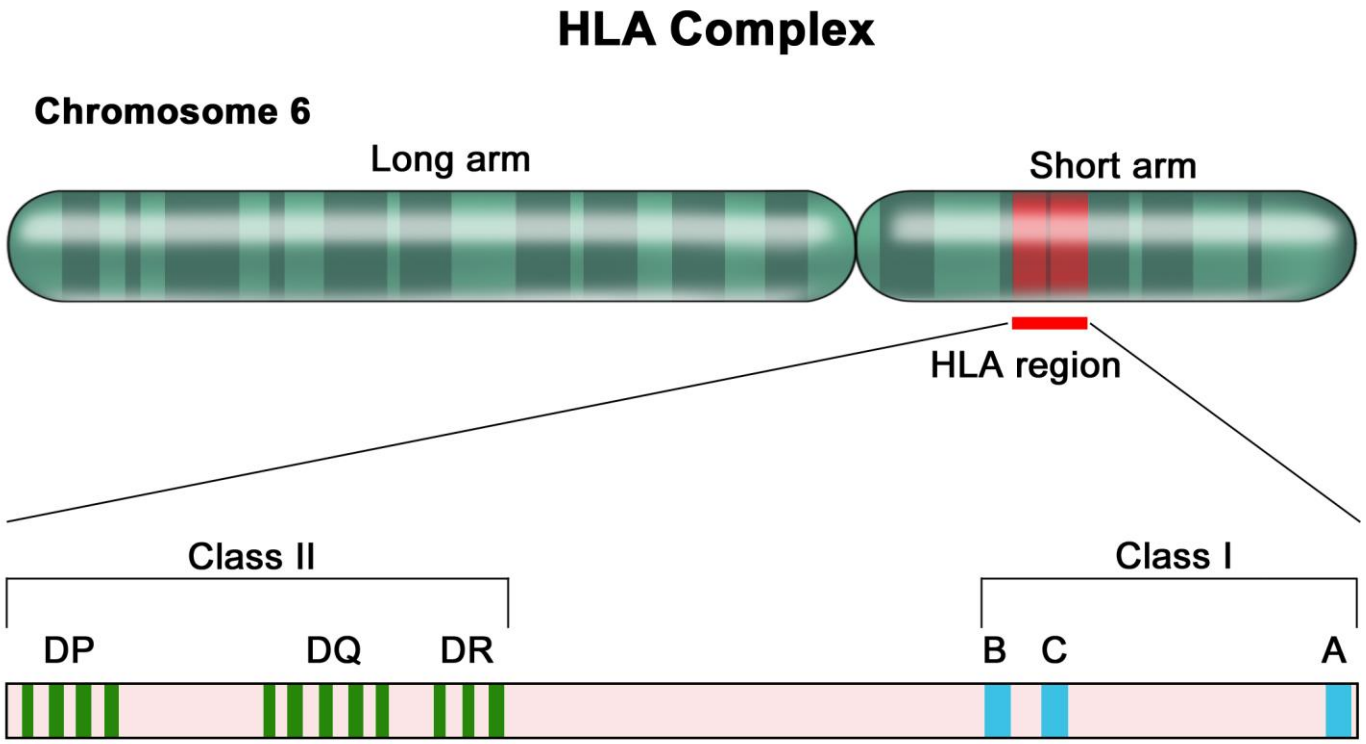
CNS, central nervous system; MRI, magnetic resonance imaging; RRMS, relapsing–remitting multiple sclerosis

1. Barkhof F et al., 1992; 2. Kappos L et al., 1999

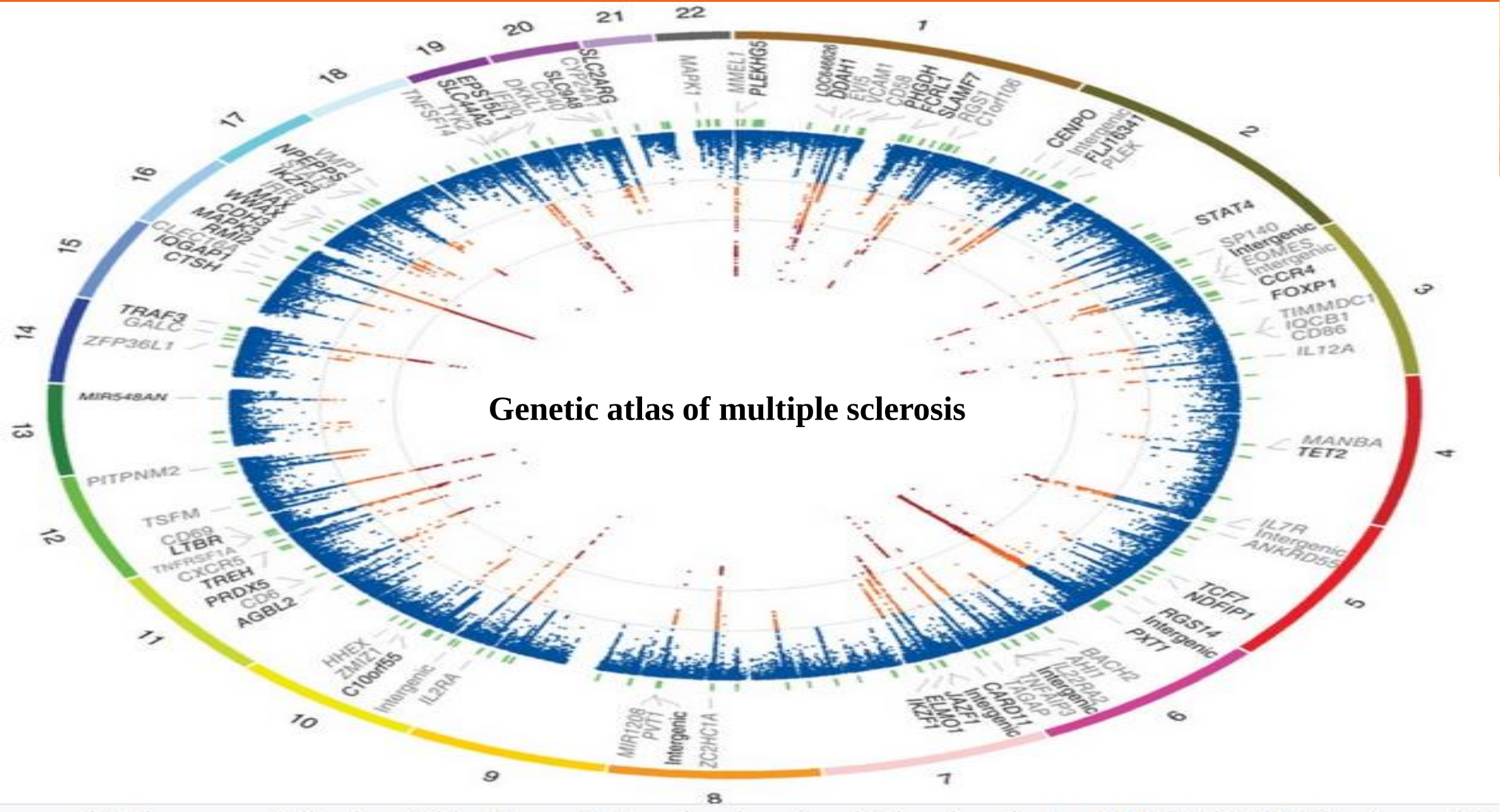
Figure adapted with permission from Oxford PharmaGenesis from Giovannoni G et al. Brain health: time matters in multiple sclerosis. © 2015 Oxford PharmaGenesis Ltd. Available at: www.msbrainhealth.org

Molecular Mechanism

Molecular Mechanisms



https://www.google.com/search?q=multiple+sclerosis **dated on Dec.9.2018**



The circus plot summarizes all the known MS-associated risk loci. https://www.ncbi.nlm.nih.gov/books/NBK470155, Dated on Dec. 25.2018

Molecular Mechanisms

- in MS:

Microglia activated & polarized + Produce of toxic factors

=

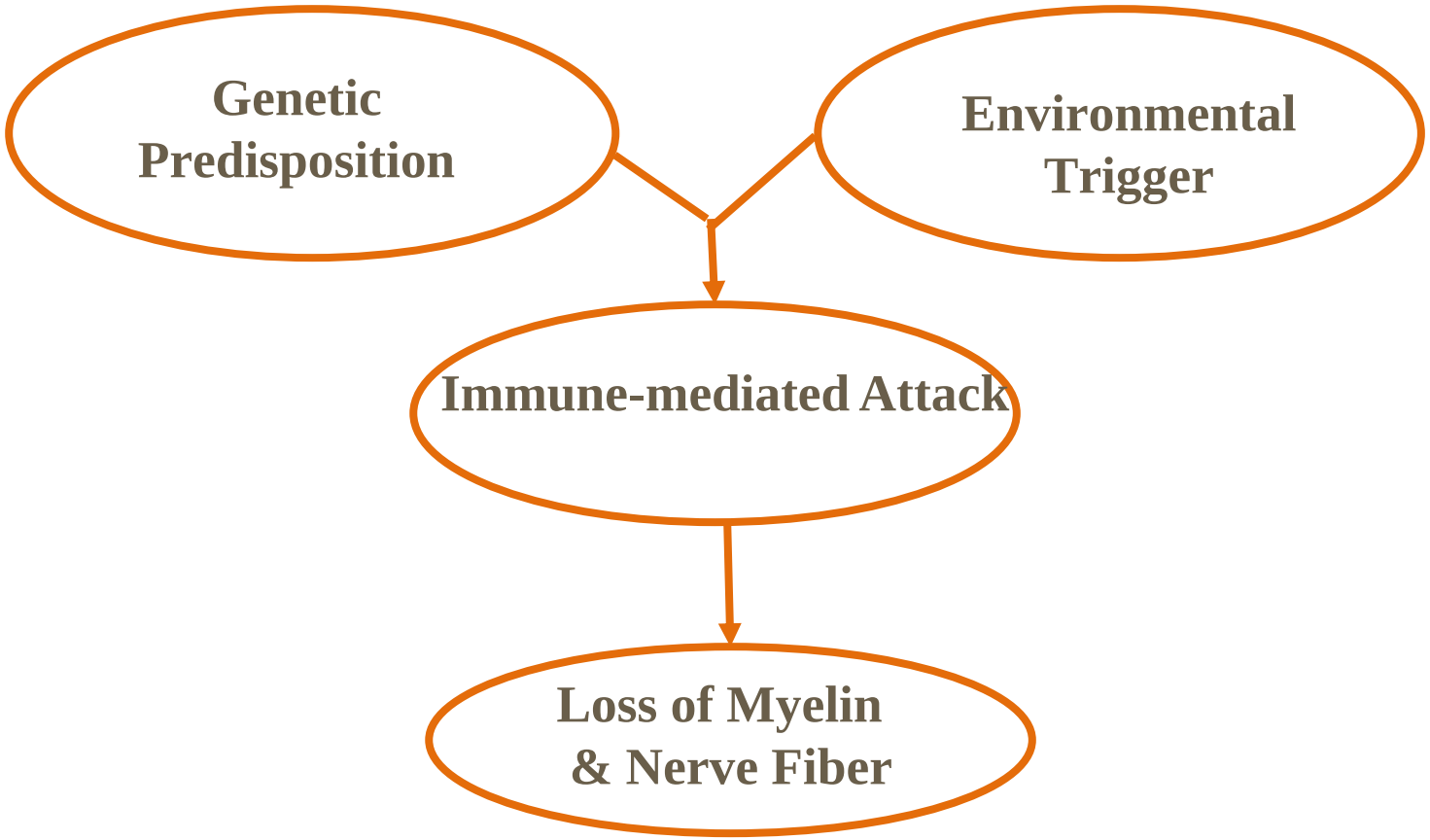
Oligodendrocyte damage

***

In addition, the **phagocytotic function** of **microglia** would directly cause **oligodendrocyte loss**

Etiology

Etiology


Genetic Predisposition
Environmental Trigger
Immune-mediated Attack
Loss of Myelin & Nerve Fiber

Etiology

Hum Genet (2017) 136:705–714
DOI 10.1007/s00439-017-1784-9

CrossMark

ORIGINAL INVESTIGATION

Common genetic etiology between "multiple sclerosis-like" single-gene disorders and familial multiple sclerosis

Anthony L. Traboulsee[1] · A. Dessa Sadovnick[1,2] · Mary Encarnacion[2] · Cecily Q. Bernales[2] · Irene M. Yee[2] · Maria G. Criscuoli[2] · Carles Vilariño-Güell[2]

23 March 2017

Received: 12 December 2016 / Accepted: 18 March 2017 / Published online: 23 March 2017

Table 1 Genes causing Mendelian diseases with clinical symptoms overlapping with MS based on Weisfeld-Adams et al. (2015)

Disorders of lysosomal storage and peroxisomal function	
ABCD1	Adrenoleukodystrophy
ARSA	Metachromatic leukodystrophy
GALC	Krabbe disease
GLA	Fabry disease
NPC1	Niemann–Pick disease, type C
NPC2	Niemann–Pick disease, type C
LYST	Chediak–Higashi syndrome
Non-metabolic leukodystrophies and leukoencephalopathies	
GFAP	Alexander disease
LMNB1	Leukodystrophy
DARS2	Leukoencephalopathy
CSF1R	Leukoencephalopathy
CLCN2	Leukoencephalopathy
GJB1	Charcot–Marie–Tooth neuropathy
NOTCH3	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy
HTRA1	Cerebral arteriopathy with subcortical infarcts and leukoencephalopathy

16 April 2018

International Journal of
Molecular Sciences

MDPI

Demyelination in Multiple Sclerosis: Reprogramming Energy Metabolism and Potential PPARγ Agonist Treatment Approaches

Alexandre Vallée [1,*], Yves Lecarpentier [2], Rémy Guillevin [3] and Jean-Noël Vallée [4,5]

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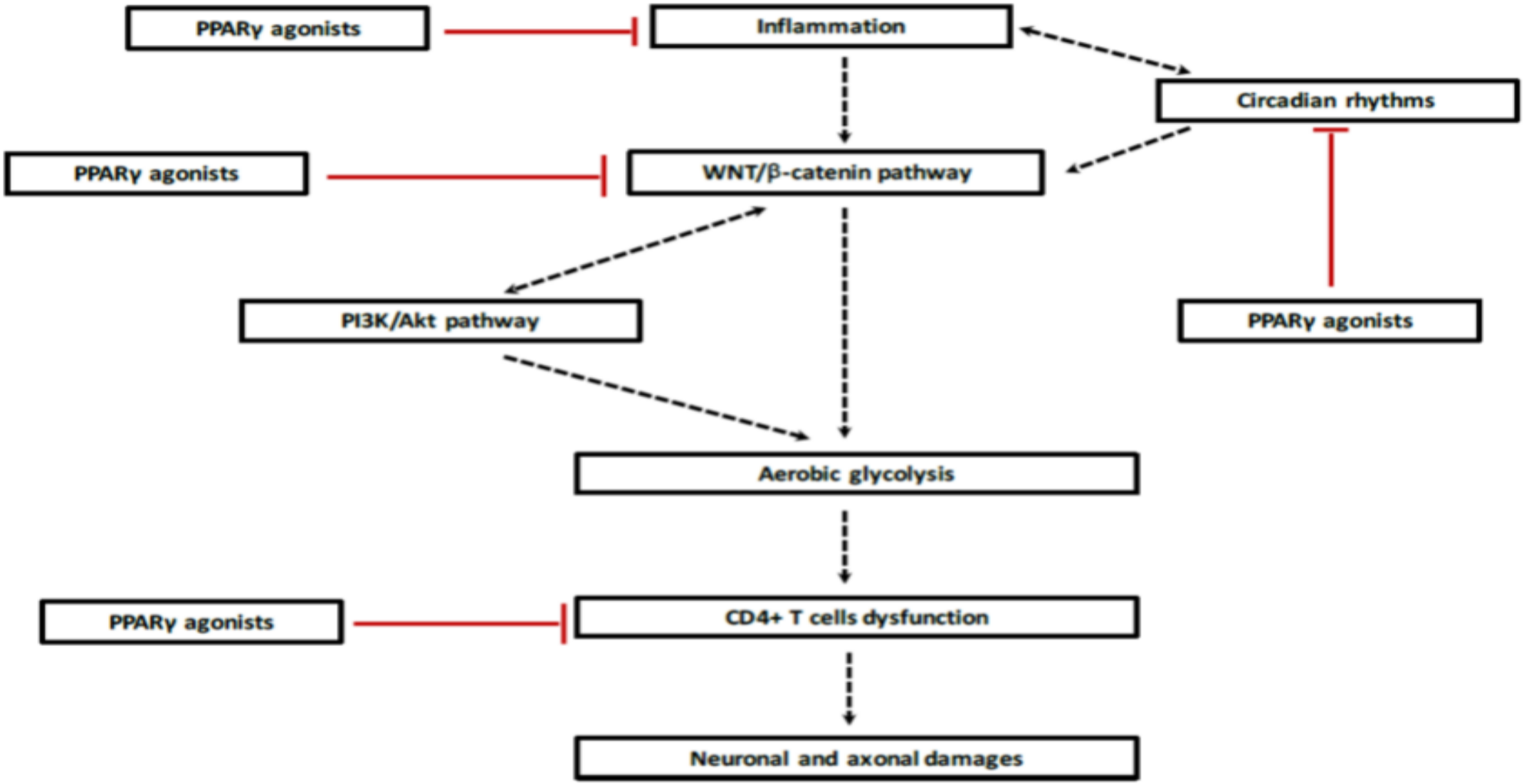
3 Data Analysis and Computations Through Imaging Modeling-Mathématiques (DACTIM), Unité mixte de recherche (UMR), Centre National de la Recherche Scientifique (CNRS) 7348 (Laboratoire de Mathématiques et Application), University of Poitiers, Centre Hospitalier Universitaire (CHU) de Poitiers, 86000 Poitiers, France; remy.guillevin@chu-poitiers.fr
4 Centre Hospitalier Universitaire (CHU) Amiens Picardie, University of Picardie Jules Verne (UPJV),



Potential PPARγ agonists treatment approach in demyelination

frontiers in Immunology

ORIGINAL RESEARCH
published: 18 May 2017
doi: 10.3389/fimmu.2017.00531

18 May 2017

Elevated Levels of Proinflammatory Cytokines in Cerebrospinal Fluid of Multiple Sclerosis Patients

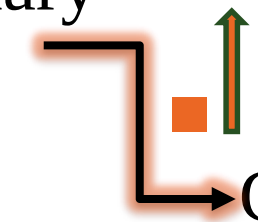
Timur Khaibullin[1], Vilena Ivanova[2], Ekaterina Martynova[2], Georgy Cherepnev[3], Farit Khabirov[1], Evgenii Granatov[1], Albert Rizvanov[2] and Svetlana Khaiboullina[2,4]**

[1] Republican Clinical Neurological Center, Kazan, Russia, [2] Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, Republic of Tatarstan, Russian Federation, [3] University Kazan Clinic, Kazan Federal University, Kazan, Republic of Tatarstan, Russian Federation, [4] Nevada Center for Biomedical Research, Reno, NV, USA

Elevated Levels of Proinflammatory Cytokines (Methods)

- Mean **age** 38 ± 2.8
- **Gender** (F/M) 15/5
- Ms. diagnosis: Remitting **16** Primary, progressing **1,** Secondary progressing **3**
- **Treatment**: MDT: **5**, IFNβ: **6**, Glatiramer acetate: **2**, None: **7**

- cytokines analyzed



IL-2RA, CCL5, CCL11, CXCL1, CXCL10, CXCL12, MIF, IFNγ

Elevated Levels of Proinflammatory Cytokines

- **CD8+** and **Th1 lymphocytes** playing a **central role** in MS brain pathology
- increased levels of **IFNγ** were found together with **CCL5**
- a strong **connection** between these cytokines, with **IFNγ** central to activating **CCL5**
- the **CCL5** interaction with **CCL27**

Volume 2018, Article ID 8168717, 17 pages
https://doi.org/10.1155/2018/8168717

Review Article

Gut Microbiota in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis: Current Applications and Future Perspectives

Fengna Chu,[1] **Mingchao Shi**,[1] **Yue Lang**,[1] **Donghui Shen**,[1] **Tao Jin**,[1] **Jie Zhu**,[1,2] **and Li Cui**[1]

[1]*Department of Neurology and Neuroscience Center, The First Hospital of Jilin University, Changchun, Jilin Province, China*
[2]*Department of Neurobiology, Care Sciences & Society, Division of Neurodegeneration, Karolinska Institutet and Karolinska University Hospital Huddinge, Stockholm, Sweden*

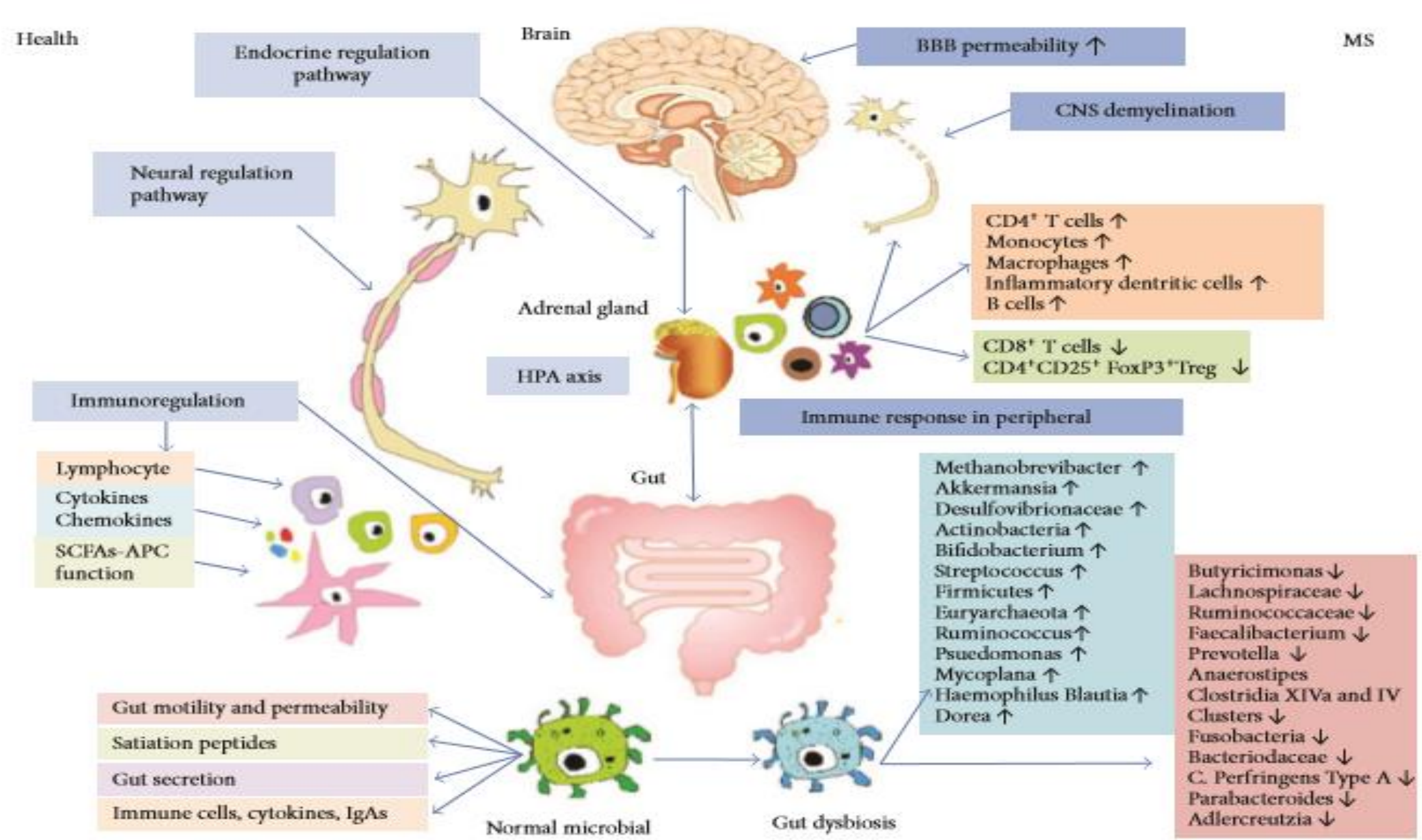
Correspondence should be addressed to Jie Zhu; jie.zhu@ki.se and Li Cui; chuili1967@126.com

Received 25 October 2017; Revised 22 February 2018; Accepted 4 March 2018; Published 2 April 2018

Academic Editor: Ronald Gladue

Normal Function of the Gut Microbiota

- **Lactic acid bacteria** can produce vitamin **B12.**
- **Bifidobacteria** are the main producers for **folate**, which is involved in **DNA synthesis** and **DNA repair.**
- **Normal flora** can systemically and locally stimulate the **development** of innate and adaptive **immune systems**



The role of the gut microbiota in health and MS

International Journal of
Molecular Sciences

MDPI

Review

The Role of Macrophages in Neuroinflammatory and Neurodegenerative Pathways of Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis: Pathogenetic Cellular Effectors and Potential Therapeutic Targets

Santa Mammana [1,2], Paolo Fagone [1], Eugenio Cavalli [1,2], Maria Sofia Basile [1], Maria Cristina Petralia [1,3], Ferdinando Nicoletti [1], Placido Bramanti [2] and Emanuela Mazzon [2,*]

1 Department of Biomedical and Biotechnological Sciences, University of Catania, 95123 Catania, Italy; santa84ma@libero.it (S.M.); paolofagone@yahoo.it (P.F.); eugeniocavalli9@hotmail.it (E.C.); sofiabasile@hotmail.it (M.S.B.); m.cristinapetralia@gmail.com (M.C.P.); ferdinic@unict.it (F.N.)
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Received: 23 February 2018; Accepted: 12 March 2018; Published: 13 March 2018

OLIGOCLONAL IgG BANDS (OCB) IN THE PATHOLOGY OF MS

- **IgGs** are produced by the immune system to fight infection

↓

Cross the blood brain barrier

↓

Attack the myelin sheath

↓

Inflammation of the CNS

Diet

Nutrition is : a possible factor in the pathogenesis of the neurological disease multiple sclerosis (MS).

Nutrition intervention studies suggest that diet may be considered as a complementary treatment to control the progression of the disease.

vitamin D deficiency in serum is a risk factor for MS and therefore a potential biomarker of MS

Vitamin B-12 has roles in CNS function (the methionine synthase–mediated conversion of homocysteine to methionine) which is essential for DNA and RNA synthesis

Diagnosis

Diagnosis

- MS is a clinical diagnosis:
  - Signs and symptoms (cognitive impairment)
  - Medical history
  - Laboratory tests
- Requires “dissemination in time and space”:
  - Space: Evidence of scarring (plaques) in at least two separate areas of the CNS
  - Time: Evidence that the plaques occurred at different points in time

What tests may be used to help confirm the diagnosis?

- Magnetic resonance imaging (MRI)
- Visual evoked potentials (VEP)
- Lumbar puncture
- Nano diagnostic neuro imaging
- Biomarkers → Osteopontin (OPN)

PLOS ONE

Jan. 18. 2018

RESEARCH ARTICLE

Osteopontin (OPN) as a CSF and blood biomarker for multiple sclerosis: A systematic review and meta-analysis

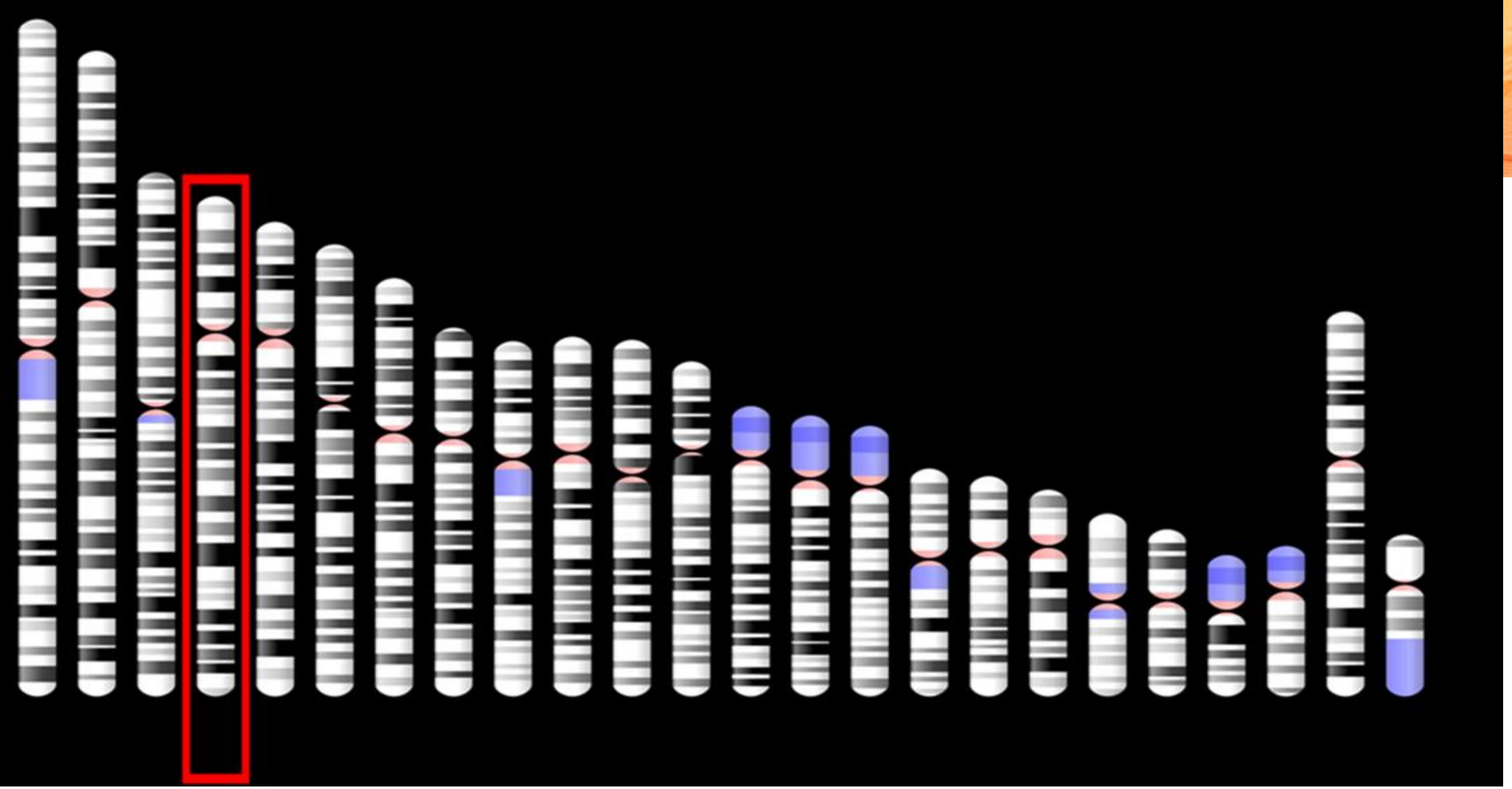
Elmira Agah[1,2], Arshia Zardoui[1,2☯], Amene Saghazadeh[3,4☯], Mona Ahmadi[5], Abbas Tafakhori[2,5*], Nima Rezaei[3,6*]

1 Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran, **2** NeuroImmunology Research Association (NIRA), Universal Scientific Education and Research Network (USERN), Tehran, Iran, **3** Research Center for Immunodeficiencies (RCID), Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran, **4** Systematic Review and Meta-analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Boston, MA, United States of America, **5** Iranian Center of Neurological Research (ICNR), Tehran University of Medical Sciences, Tehran, Iran, **6** Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

☯ These authors contributed equally to this work.
* a_tafakhori@sina.tums.ac.ir (AT); rezaei_nima@tums.ac.ir (NR)

Function of OPN:

- bone remodeling
- wound healing
- cancer biology
- vascular disorders
- inflammatory diseases
- Expressed in immune cells



https://en.wikipedia.org/wiki/Osteopontin dated on Dec. 12. 2018

Therapy

Therapy

Non Molecular:

- Drugs or Disease Modifying Drugs (DMD)
- Nano Medicines
- Stem-cell Therapy
- Trans-Differentiation
- Immunotherapy
- Worm Therapy
- Zinc Aspartate & IVIGs

Molecular :

- DNA Aptamer
- CD49d antisense
- MicroRNAs
- Gene Therapy

Drug	Brand name	Dosage and Route of Administration	Mechanism of action
Interferon b-1b Betaseron,	Interferon b-1b Betaseron,	250 mg, SC, every other day	Suppresses expression of inflammatory cytokines, Down regulation of costimulatory molecules like CD 80, CD 40 om Antigen presenting cells, inhibits T cell activation
Interferon b-1a Avonex	Interferon b-1a Avonex	30 mg, IM, once a week	Same as interferon b-1b
Oldest			
Newest			
Alemtuzumab	Lemtrada	IV infusion for 5 consecutive days, than for 3 consecutive days 1 year later	Depletes B-cells, T- cells, monocytes, macrophages and dendritic cells.
Peg interferon b-1a	Plegridy	125 mg, SQ, once every two weeks	Same as interferon b-1b

Table 1: List of FDA approved drugs// S. Ojha, B. Kumar / Journal of Cellular Immunotherapy dated on 2018

Therapy

Therapeutic Monoclonal Antibodies

- CD20 antibodies → To target B-cells
- Rituximab, Orelizumab, Ofatumumab, Declizumab → Cytokine/IL-2 receptor (CD25)
- Alemtuzumab → Anti-CD52 monoclonal antibody
- Natalizumab → Anti-α4 integrin antibody

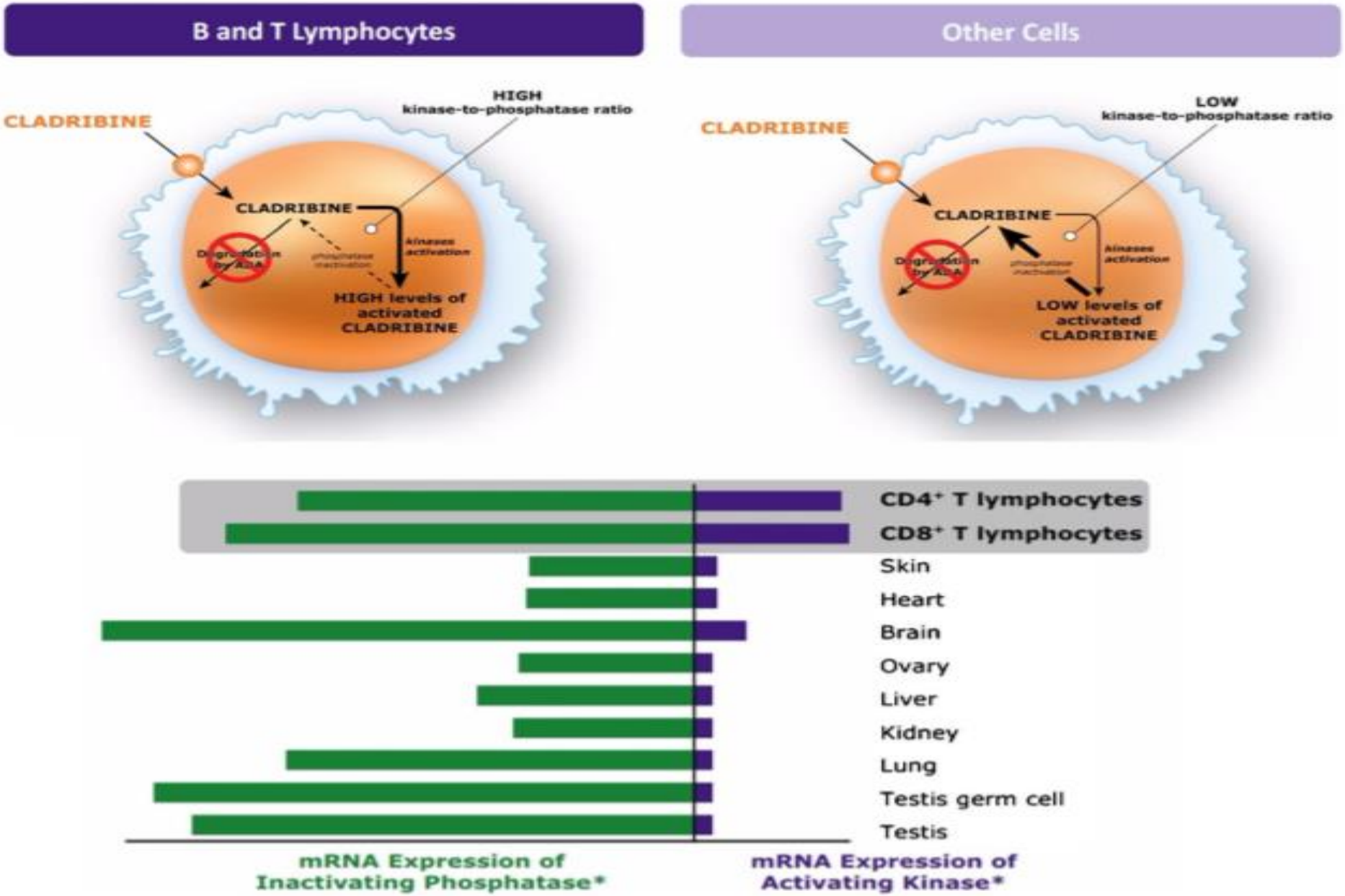
Immune modulators

- ✓ IFN/IFN + statins, Teriflunomide → Inhibits proliferation of activated T- and B-cells
- ✓ Mitoxantrone, Dimethyl fumarate → NF-κB inhibition and inhibition of pro-inflammatory cytokines
- ✓ Glatiramer acetate, Fingolimod → Inhibits release of lymphocytes from lymphoid tissues induction of miRNAs

Therapy

Cladribine:

- An Adenosine analogue
- **Enter** cells via specific **nucleoside transporter proteins**
- as a prodrug
- its **activity** is **dependent** on the **intracellular accumulation** of its active triphosphate



The accumulation of active Cladribine (2-CdATP) is dependent on the ratio of deoxycytidine kinase

Nano-medicines
Summary of recent patents against MS

- Yechezkel Barenholz et al. (2008) → Pharmaceutical **Liposomal** formulation
- Josbert Maarten Metselaar et al. (2010) → non charged **vesicle** forming lipids derivatised with polyethylene glycol
- Sergey Sergeevich Avtushenko et al. (2011) → tetramannosyl-3-L-lysinedioleoyl glycerol & 2, 3-dipalmitoyl-glycerol-1-phosphatydyl choline, and also includes some oligopeptides
- Yechezkel Barenholz et al. (2015) → Orglucocorticoid derivative which is encapsulated in a liposome

doi:10.1093/brain/awx154 BRAIN 2017: 140; 2776–2796 | 2776

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW ARTICLE

Cell-based therapeutic strategies for multiple sclerosis

Neil J. Scolding,[1] Marcelo Pasquini,[2] Stephen C. Reingold[3] and Jeffrey A. Cohen[4] on behalf of attendees at the International Conference on Cell-Based Therapies for Multiple Sclerosis

The availability of multiple disease-modifying medications with regulatory approval to treat multiple sclerosis illustrates the substantial progress made in therapy of the disease. However, all are only partially effective in preventing inflammatory tissue damage in the central nervous system and none directly promotes repair. Cell-based therapies, including immunoablation followed by autologous haematopoietic stem cell transplantation, mesenchymal and related stem cell transplantation, pharmacologic manipulation of endogenous stem cells to enhance their reparative capabilities, and transplantation of oligodendrocyte progenitor cells, have generated substantial interest as novel therapeutic strategies for immune modulation, neuroprotection, or repair of the damaged central nervous system in multiple sclerosis. Each approach has potential advantages but also safety concerns and unresolved questions. Moreover, clinical trials of cell-based therapies present several unique methodological and ethical issues. We summarize here the status of cell-based therapies to treat multiple sclerosis and make consensus recommendations for future research and clinical trials.

Stem cells and their mode of function and potential in therapy

Stem Cell Type	Mode of Function/Signalling Pathways
Mesenchymal stem cells	Modulation of the immune system Inhibition of T-cells, B-cells and NK cells
Hematopoietic stem cells	NF-κB STAT
Neural stem cells	Replacement therapy

International Journal of *Molecular Sciences*

MDPI

Review

Novel Therapeutics for Multiple Sclerosis Designed by Parasitic Worms

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Abstract: The evolutionary response to endemic infections with parasitic worms (helminth) was the development of a distinct regulatory immune profile arising from the need to encapsulate the helminths while simultaneously repairing tissue damage. According to the old friend's hypothesis, the diminished exposure to these parasites in the developed world has resulted in a dysregulated immune response that contributes to the increased incidence of immune mediated diseases such as Multiple Sclerosis (MS). Indeed, the global distribution of MS shows an inverse correlation to the prevalence of helminth infection. On this basis, the possibility of treating MS with helminth infection has been explored in animal models and phase 1 and 2 human clinical trials. However, the possibility also exists that the individual immune modulatory molecules secreted by helminth parasites may offer a more defined therapeutic strategy.

Specialty Pharmacy Times
Fresh Information Every Day

Brain Lymphatic Vessels May Serve as Potential Target for MS Treatment

Jennifer Barrett, Associate Editor
Publish Date: Monday, October 01, 2018

New research has found that lymphatic vessels surrounding the brain may play a crucial role in the development and progression of multiple sclerosis (MS). The vessels may also play a key role in other neuro-inflammatory diseases and brain infections as well.

Researchers from the University of Virginia School of Medicine found that the vessels appear to carry previously unknown messages from the brain to the immune system that ultimately trigger the symptoms of MS.

Brain's lymphatic vessels

- By **targeting the lymphatic vessels surrounding the brain**, the researchers were able to **impede the development of MS** in a mouse model using a number of strategies to block or destroy the vessels, effectively decreasing the amount of destructive immune cells capable of causing paralysis.

- **During inflammation**, they did not change in size or complexity much, but what was really exciting to discover they allowed **whole immune cells** to **traffic** through them.

Blocking the cells in mice seemed to be beneficial…

Hindawi
Journal of Immunology Research
Volume 2018, Article ID 5982169, 7 pages
https://doi.org/10.1155/2018/5982169

Research Article

Combined Treatment with Zinc Aspartate and Intravenous Immunoglobulins (IVIGs) Ameliorates Experimental Autoimmune Encephalomyelitis (EAE)

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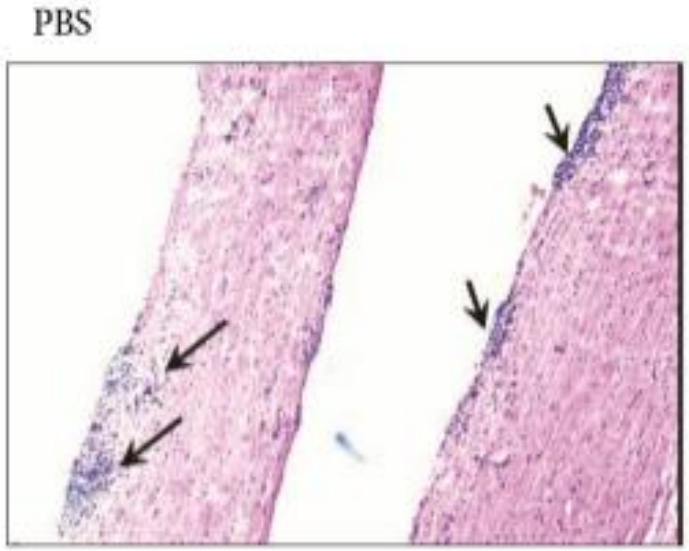
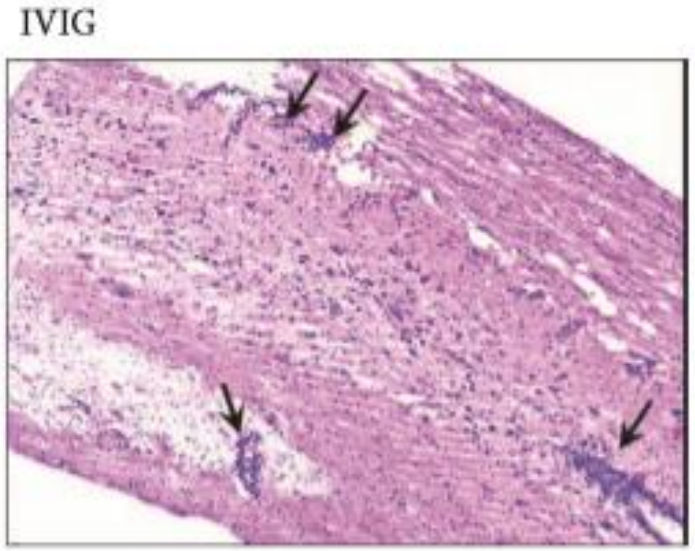
- Results:

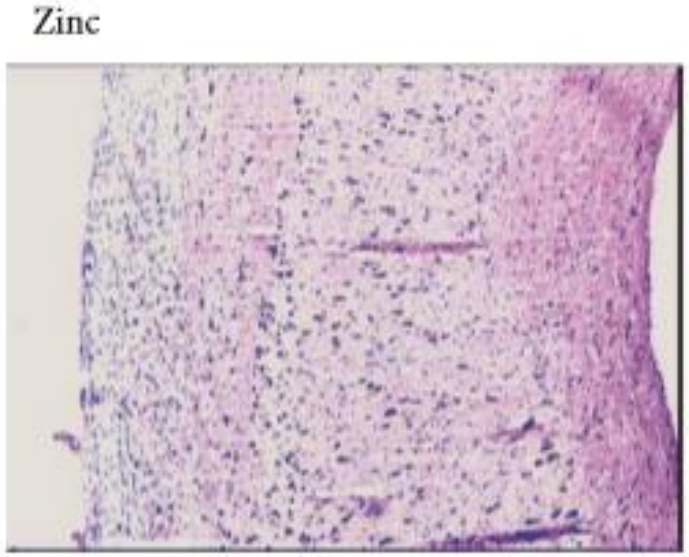
Influence of Preventive and Therapeutic Application of IVIG

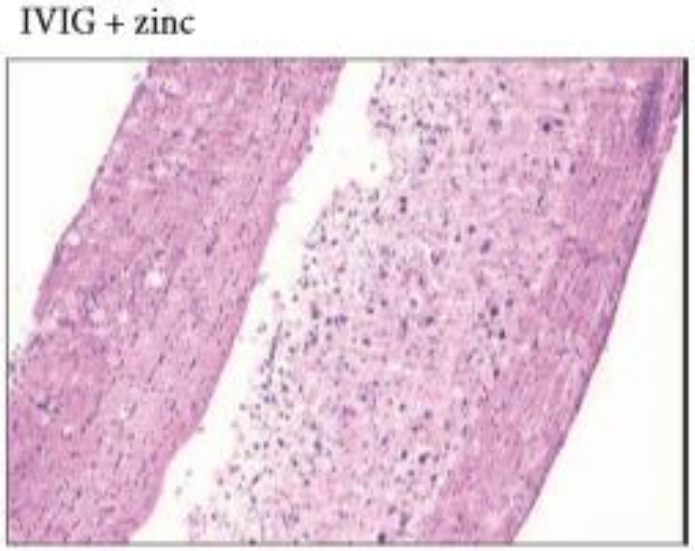
Effects of Therapeutic Application of IVIG, Zinc Aspartate

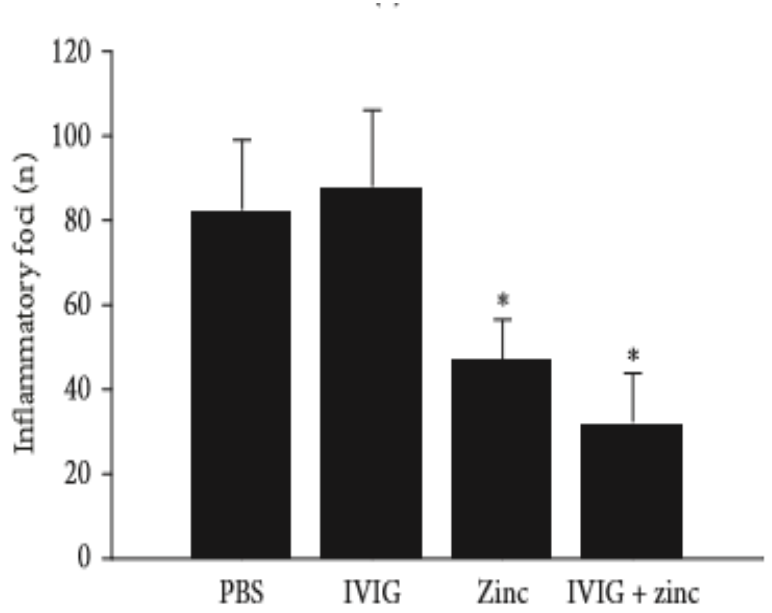
the Combination of Both











Effect of therapeutic application of IVIG, zinc aspartate, and the combination of both on formation of inflammatory lesions in the CNS of EAE mice

Remyelination Induced by a DNA Aptamer in a Mouse Model of Multiple Sclerosis

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1 Department of Biochemistry and Molecular Biology, Mayo Clinic College of Medicine, Rochester, Minnesota, United States of America, **2** Departments of Neurology and Immunology, Mayo Clinic College of Medicine, Rochester, Minnesota, United States of America

June 27, 2012

Abstract

Multiple sclerosis (MS) is a debilitating inflammatory disease of the central nervous system (CNS) characterized by local destruction of the insulating myelin surrounding neuronal axons. With more than 200 million MS patients worldwide, the absence of treatments that prevent progression or induce repair poses a major challenge. Anti-inflammatory therapies have met with limited success only in preventing relapses. Previous screening of human serum samples revealed natural IgM antibodies that bind oligodendrocytes and promote both cell signaling and remyelination of CNS lesions in an MS model involving chronic infection of susceptible mice by Theiler's encephalomyelitis virus and in the lysolecithin model of focal demyelination. This intriguing result raises the possibility that molecules with binding specificity for oligodendrocytes or myelin components may promote therapeutic remyelination in MS. Because of the size and complexity of IgM antibodies, it is of interest to identify smaller myelin-specific molecules with the ability to promote remyelination *in vivo*. Here we show that a 40-nucleotide single-stranded DNA aptamer selected for affinity to murine myelin shows this property. This aptamer binds multiple myelin components *in vitro*. Peritoneal injection of this aptamer results in distribution to CNS tissues and promotes remyelination of CNS lesions in mice infected by Theiler's virus. Interestingly, the selected DNA aptamer contains guanosine-rich sequences predicted to induce folding involving guanosine quartet structures. Relative to monoclonal antibodies, DNA aptamers are small, stable, and non-immunogenic, suggesting new possibilities for MS treatment.

CD49d Antisense (Molecular)

The monoclonal antibody **Natalizumab** **targets** the adhesion molecule very late antigen 4 (**VLA-4**)*

Interfere with the **transmigration** of **leukocytes** into the **CNS**

so

Reduces brain lesions

*VLA-4 = has a role in the maturation, apoptosis, activation, adhesion, and migration of B and T cells

CD49d Antisense (Molecular)

ATL1102 → second-generation **antisense oligonucleotide** to **CD49d RNA****

→ binds CD49d RNA by Watson-Crick base pairing

→ **reduces** CD49d RNA and VLA-4 **expression**

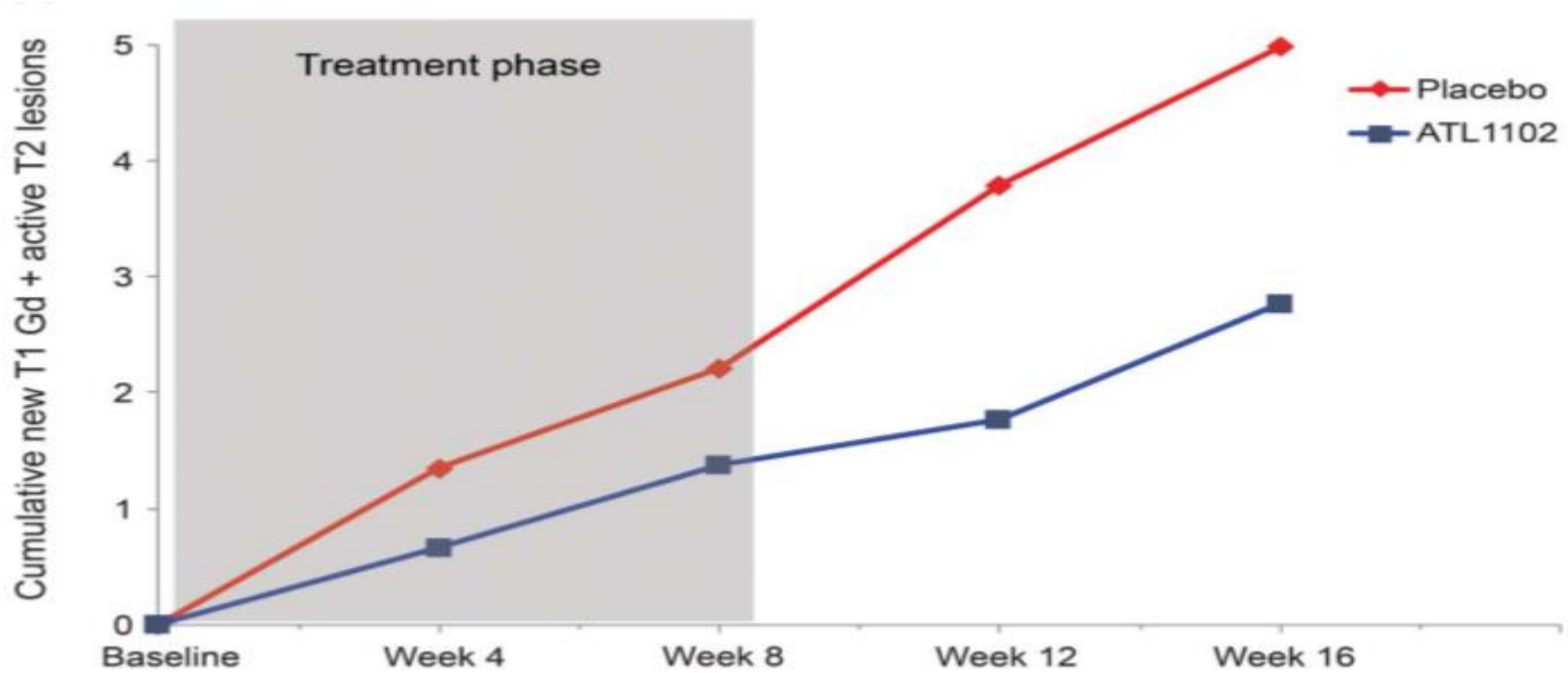
***

Reduction in the number of **CD19**, **B cells** with of **VLA-4 expression**

****CD49d RNA = the a chain of VLA-4.**

CD49d Antisense (Molecular)

- VLA-4, has a **role** in the **maturation**, **apoptosis**, **activation**, **adhesion**, and **migration** of **B** and **T** cells.



Cumulative number of new active lesions, which is treated with ATL 1102 (this picture is gotten from https://www.ncbi.nlm.nih.gov/pubmed dated on Dec. 8. 2018)

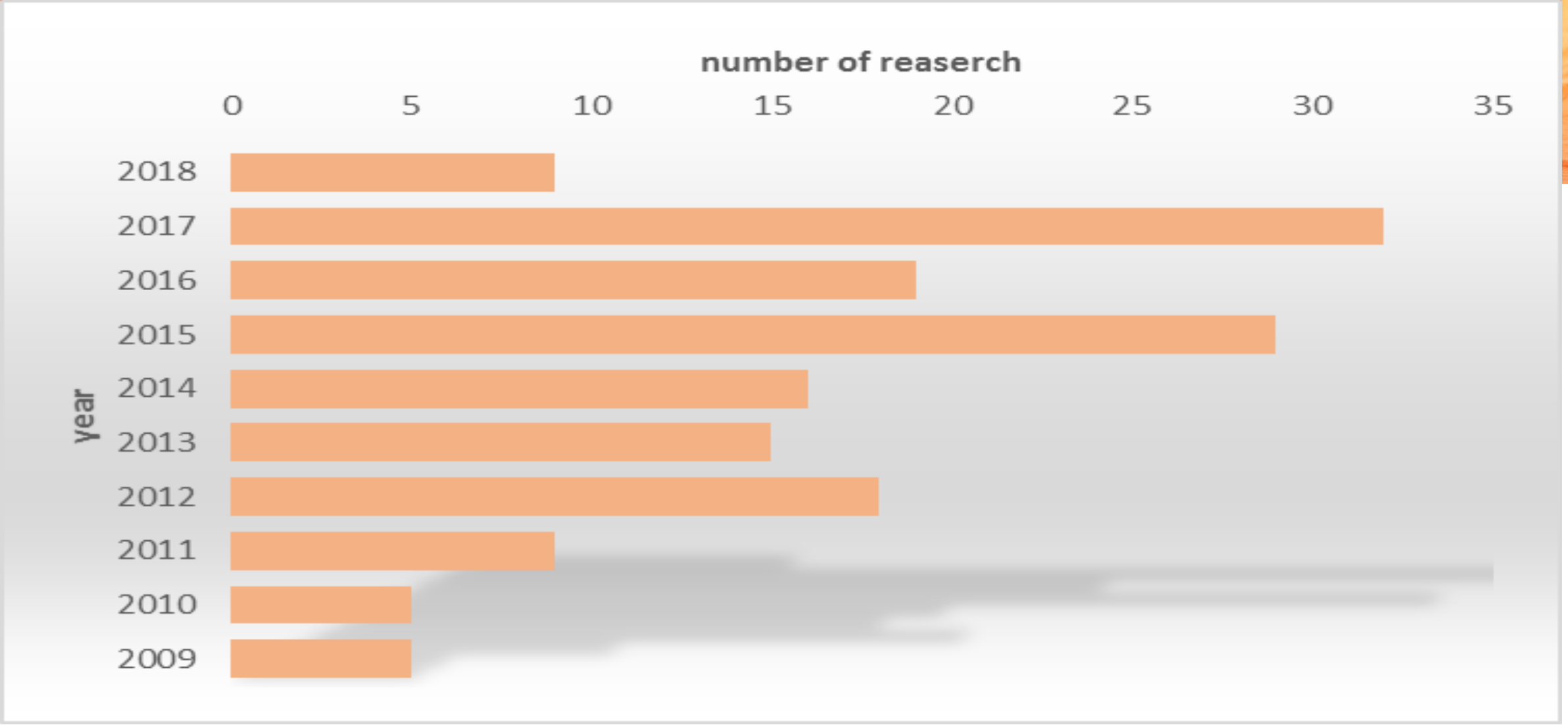
MicroRNAs in Multiple Sclerosis

- MicroRNAs (miRNAs):

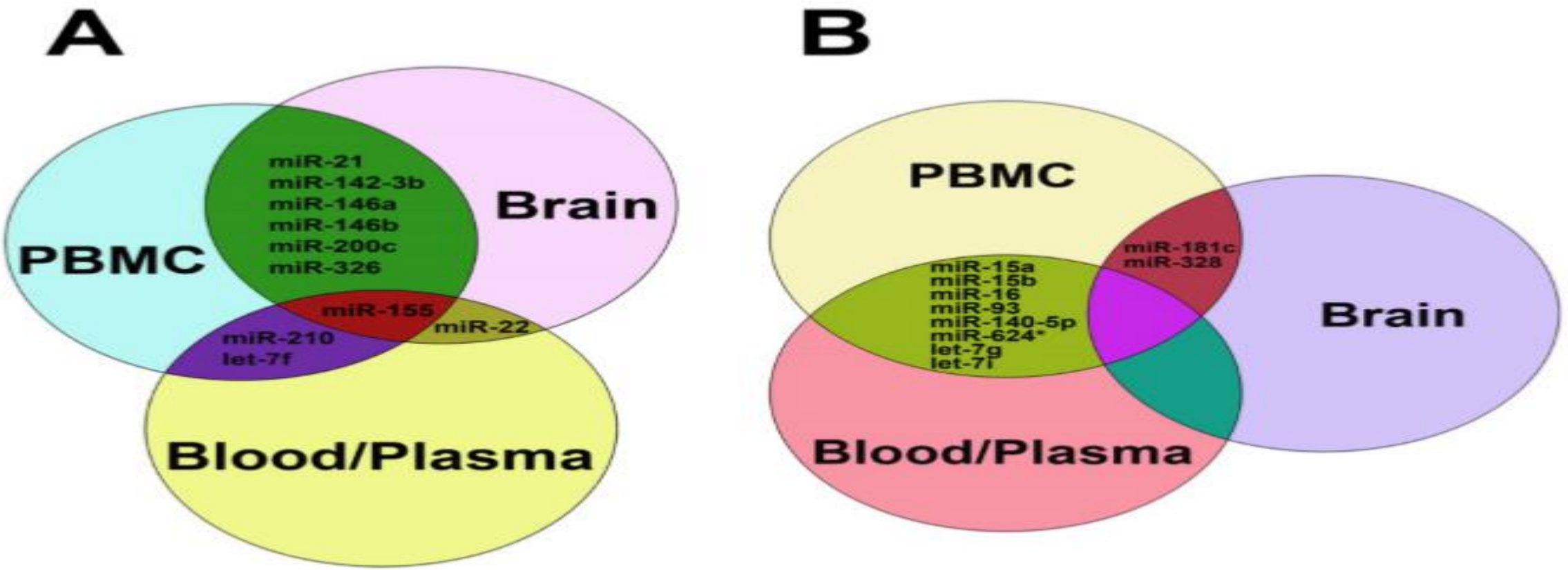
↑ miR-21, miR-142-3p, miR-146a, miR-146b, miR-155 & miR-326

↓ miR-15a, miR-15b, miR-181c & miR-328

As diagnostic markers & therapeutic targets: <u>miR-326</u>, <u>miR-155</u>



Estimation of number of publications about studies on miRNAs in MS yearly from 2009 to 2018. Based on the retrieved papers from the PUBMED database after searching related references by means of miRNA, multiple and sclerosis key words, the number of publications about the studies on miRNAs in MS were calculated.



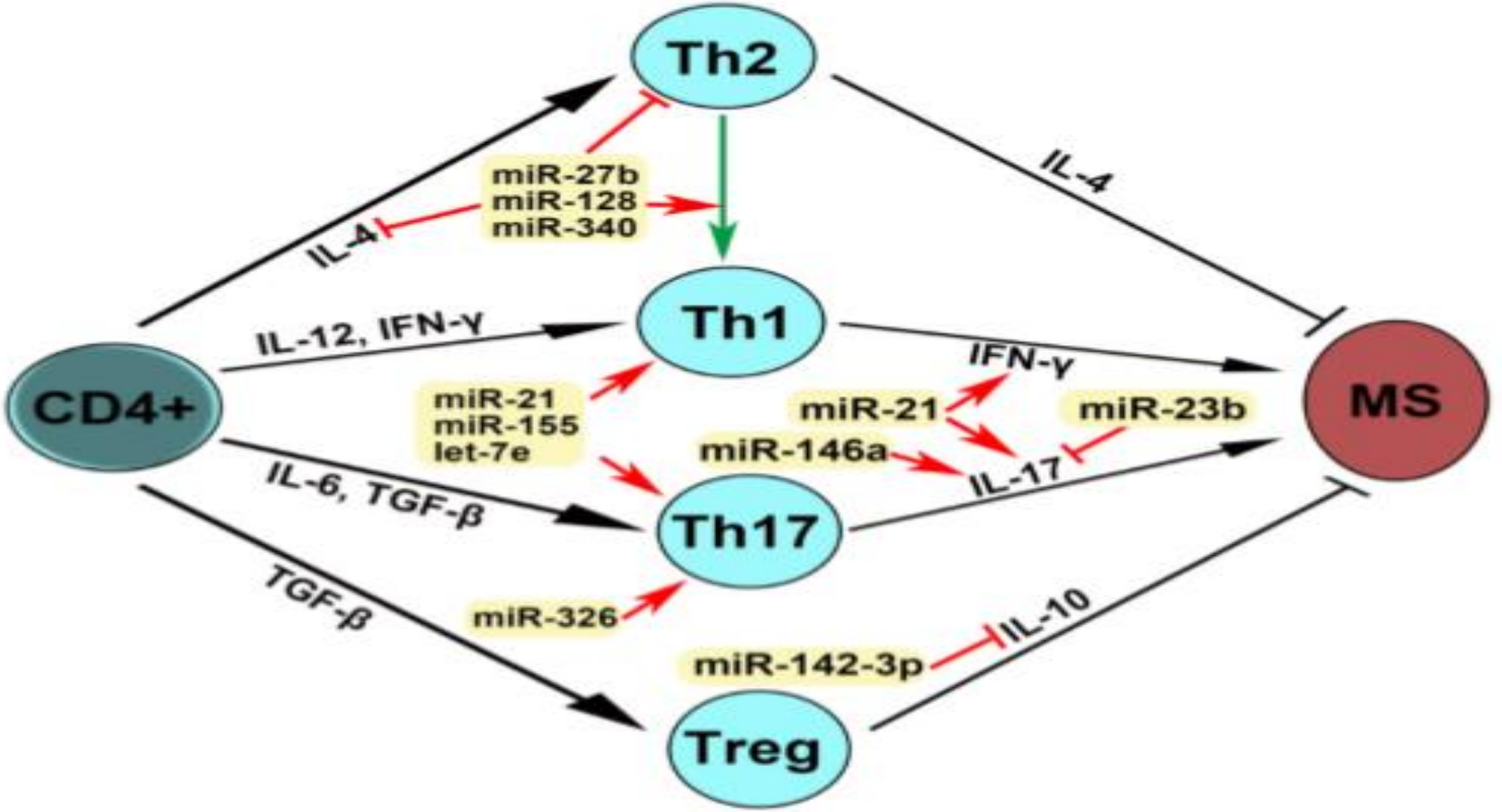
miR-155 was up-regulated among PBMC, brain and blood/plasma

miR-181c and miR-328 were down-regulated in both brain and blood/plasma.

International journal of Medical science, 2014; 11(8): 810-818 , dated on Dec. 10. 2018

❑ miRNAs as MS Therapeutic Targets:

- ✓ **Suppression** of **miR-155** expression ⊘ the development of **Th1** and **Th17** cells.
- ✓ **miR-326** expression **increased** significantly in active MS lesions.
- ✓ **miR-23b** expression ⊘ **IL-17** ,**TNF-α**, **TGF-β**.
- ✓ **miR-124** expression increased in the **demyelinated** brain



Mechanism of action of dysregulated miRNAs in patients with MS

Molecular Therapy
Original Article

Gene Therapy-Induced Antigen-Specific Tregs Inhibit Neuro-inflammation and Reverse Disease in a Mouse Model of Multiple Sclerosis

Geoffrey D. Keeler,[1] Sandeep Kumar,[1] Brett Palaschak,[1] Emily L. Silverberg,[1] David M. Markusic,[1] Noah T. Jones,[1] and Brad E. Hoffman[1,2]

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The devastating neurodegenerative disease multiple sclerosis (MS) could substantially benefit from an adeno-associated virus (AAV) immunotherapy designed to restore a robust and durable antigen-specific tolerance. However, developing a sufficiently potent and lasting immune-regulatory therapy that can intervene in ongoing disease is a major challenge and has thus been elusive. We addressed this problem by developing a highly effective and robust tolerance-inducing in vivo gene ther-

$CD4^+CD25^+FOXP3^+$ Tregs. Numerous studies have demonstrated the power of Treg-based immunotherapies.[6,8,9] For example, it has been shown that adoptive transfer of polyclonal $CD4^+CD25^+$ Tregs can temporarily prevent or reduce the neurological symptoms of experimental autoimmune encephalomyelitis (EAE), the murine model of MS.[10] Recent clinical studies have reported that injection of $CD4^+CD25^+$ Tregs appears to be a safe and effective cellular treatment in patients with type 1 diabetes and graft-versus-host dis-

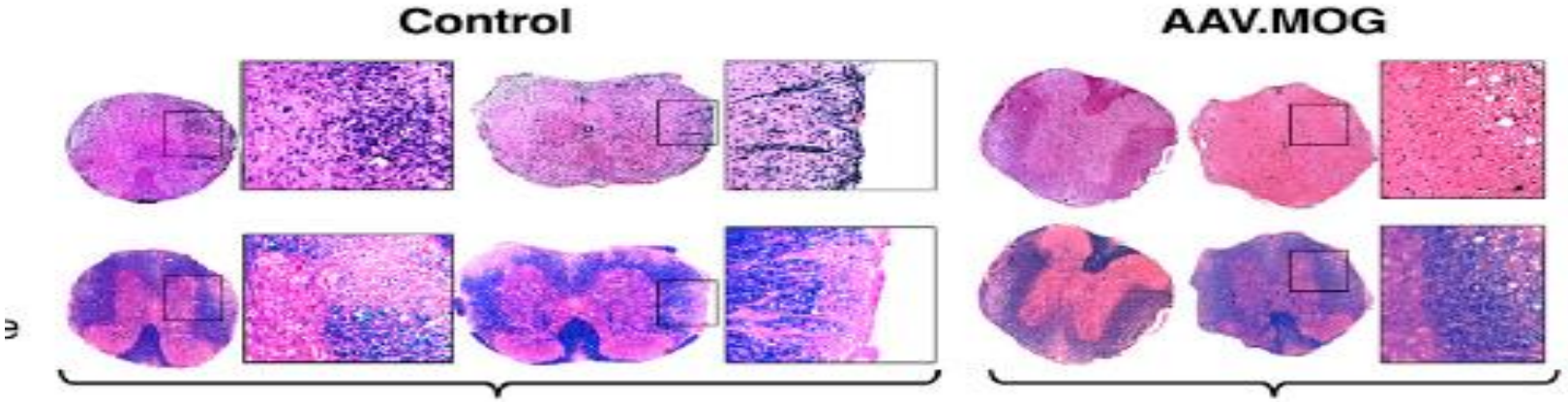
Gene Therapy

- Abnormalities in the frequency or suppressive, **CD4+CD25+FOXP3+ Tregs** cause various autoimmune diseases:

➢ engineered an **AAV8** vector to contain the full coding sequence (CDS) of the neuroprotein **MOG**

➢ placed it under control of a liver-specific promoter

➢ **By day 30, mice that received AAV8.MOG immunotherapy had a significantly greater reduction in clinical scores compared to control mice**



https://www.ncbi.nlm.nih.gov/pubmed/28943274

Gene therapy with Sox2

- Demyelinated astrocyte $\xrightarrow{\text{Sox2}}$ Oligodendrocyte Precursor into CNS:

1. Injection GFP
2. Injection GFP + Sox2

↓ **Astrocyte**

↑ **oligodendrocyte Precursor**

21 Days

Oligodendrocyte Precursor ↓ in favor of Mature oligodendrocyte

Astrocyte differentiation(specially at the time of destruction of Myelin) to **Oligodendrocyte Precursor** & **Mature oligodendrocyte**

A molecular key

- During the progressive phase: the microglial cells in the brain → responsible for the neurological deterioration
- microglial cells → react when faced with any damage or infection in it

↓

is in principle **beneficial**

but

becomes harmful when it is prolonged over time

Science News *from research organizations*

A molecular key for delaying the progression of Multiple Sclerosis is found

Date: July 20, 2018

Source: University of the Basque Country

Summary: In the lab it was possible to improve the symptoms in the chronic phase of the disease while encouraging the repair of the nervous tissue, and the challenge now is to move the research forward in humans.

Receptor **P2X4** present **in** the **microglial cells**

↓

encourage the body's own repair responses

↓

improve the symptoms during the chronic phase of the disease

Conclusion

Two key recommendations for change:

Maximize lifelong brain health

1. Minimize delays in diagnosis & treatment

2. Monitor disease activity & treat to a target

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Thanks For Your
Attention